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CANCER RESEARCH

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VOLUME 5

DECEMBER, 1945

NUMBER 12

Studies in Carcinogenesis with Azo Compounds

I. The Action of Four Azo Dyes in Mixed and Pure Strain Mice*

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(Received for publication September 4, 1945)

It has been known since 1932 (23) that 4'-amino-2,3'-azotoluene will induce liver tumors in rats receiving the dye orally. Later, Kinoshita (10) demonstrated the superior carcinogenic activity of an isomeric azo dye, N,N-dimethyl-*p*-aminoazobenzene, toward the rat liver; this superiority was revealed both in the shorter minimal feeding period and in the shorter latent period. Both these azo dyes are methyl derivatives of the base, *p*-aminoazobenzene, which was long regarded as noncarcinogenic (8, 10, 14, 21, 23, 25). Consideration of the fact that 4'-amino-2,3'-azotoluene was carcinogenic although the amino group was not substituted, and also of the inhibitory action of *p*-phenylenediamine, one of the products of reductive fission of *p*-aminoazobenzene, upon certain enzyme systems (8, 9, 20) led the present author to feed *p*-aminoazobenzene in a modified diet to rats for a long period. Unequivocal liver-cell carcinomas were found after 17 months' feeding, with metastases in one animal (11). Thus it appears that *p*-aminoazobenzene, as well as its 2,3'-dimethyl and N,N-dimethyl derivatives, is carcinogenic for the liver of rats; methylation does not confer, but does greatly enhance, carcinogenic power, provided the methyl groups enter certain positions.

Yoshida (25), and Sasaki and Yoshida (21) report having fed 2'-amino-4,5'-azotoluene for periods up to 476 days to rats without eliciting any liver tumors. Although Sasaki and Yoshida provide a structural formula for their compound that would show it to be 5'-amino-2,2'-azotoluene, and Cook and Kennaway (5) depict it as 4'-amino-2,2'-azotoluene, Miura (16), summarizing the experiments of Sasaki and Yoshida,

depicts the compound as 2'-amino-4,5'-azotoluene; this identity is accepted by Hartwell (7).

The only reference to tests with *p*-aminoazobenzene in mice is made by Yoshida (24), who gave subcutaneous injections of a 10 per cent solution in olive oil, but as no mice seem to have survived beyond 23 days this was hardly a test for carcinogenic activity; 2'-amino-4,5'-azotoluene does not seem to have been tested in mice. This paper deals with experiments in which azo dyes were injected subcutaneously into stock mice of mixed colors and, in the case of 2 azo dyes, into mice of the Cba and C57 black strains. The 4 azo dyes are shown in Fig. 1.

METHODS AND MATERIALS

The stock mice used were either purchased as required from a dealer or were bred in this laboratory from mice previously bought from the same dealer. The large range of coat color indicates considerable heterozygous constitution; the suitability of these mice for testing for the presence or absence of carcinogenic activity in chemical compounds has been emphasized in a previous paper from this laboratory (19). Spontaneous tumors are rare, although no precise data are available.

The Cba strain was bred in this laboratory from mice of this strain originally obtained from Dr. Greenwood, Edinburgh. The C57 black mice were bred from a pair given to us by Dr. Grüneberg, of Guy's Hospital, London.

The earliest experiment concerned only 2'-amino-4,5'-azotoluene; this dye was obtained from British Drug Houses, Ltd., and used without further purification. Subsequent work involving the other 3 dyes was carried out with materials purified by chromatography. *p*-Aminoazobenzene was obtained from British Drug Houses, Ltd.; after passage in benzene solution

* Because of the difficulties of international communication the author has not read proof of this article.

** Working under a full time grant from The British Empire Cancer Campaign.

through activated alumina, and subsequent crystallization by adding 2 volumes of petroleum ether (b.p., 60° to 80°) to the concentrated filtrate, the orange needles melted at 123° C. N,N-dimethyl-*p*-aminoazobenzene was obtained from British Drug Houses, Ltd. under the name "Dimethyl Yellow, Analar"; a quantity of the same substance under the name "Waxoline Yellow, A.D.S." was given to us by I.C.I., Ltd., Dye-stuffs Group. Both samples, after purification as above, gave orange-yellow needles melting at 117° C. 4'-Amino-2,3'-azotoluene was bought from British Drug Houses, Ltd.; purification as above yielded cerise needles melting at 101.5° C. (sintering at 99° C).

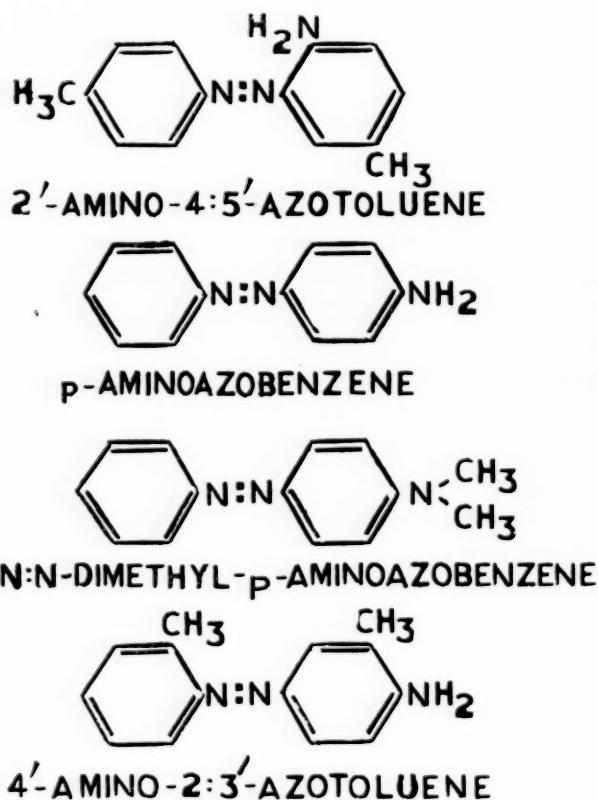


FIG. 1.—Structural formulas for azo compounds used in these experiments.

More than 1 type of diet was used in conjunction with each dye, but as the experiment with 2'-amino-4,5'-azotoluene differed from the experiment involving the other 3 dyes the details will be given under the appropriate headings.

EXPERIMENTS WITH 2'-AMINO-4:5'-AZOTOLUENE

Experimental data.—This series was begun early in 1941 and only stock mice of mixed colors were used. The dye was dissolved in olive oil and injections were made subcutaneously in the flank once a fortnight. At first 0.25 ml. of a 1 per cent solution was injected

per mouse, but the strength was increased to 2 per cent in Groups I and II after 266 days and in Groups III and IV after 238 days. The dose was further increased, by injecting 0.5 ml. of the 2 per cent solution, in Groups I and II after 366 days and in Groups III and IV after 338 days.

All 4 groups received a basal diet of rat cake (22) and water *ad libitum*. Group I were given only the basal diet, and served as controls. The other 3 groups were designed to test whether yeast had any protective action against this dye as it had been shown to have in rats injected with N,N-dimethyl-*p*-aminoazobenzene, and, if so, whether the active constituent was extractable with water or not. Group II therefore were fed powdered rat cake (85 per cent) plus dried baker's yeast (15 per cent). Group III received rat cake made to a stiff paste with a concentrated aqueous extract of similar yeast, while the residue from the extraction was given with rat cake powder, 1:3, to Group IV. Twelve mice of both sexes were used in each group except Group IV, where 6 more were added after 6 weeks to replace early losses.

Results.—As no mice in Group I developed tumors at any site, the possible protective action of yeast could not be assessed. As no tumors were seen in any groups, it can be concluded that 2'-amino-4,5'-azotoluene is noncarcinogenic for stock mice, at least when administered by the subcutaneous route, up to 472 days and up to a total dosage of 67.5 mgm. The pathological reports showed that this azo dye is not without action on the liver; at least a quarter of the mice had focal necroses there, while others had massive necrosis. There was little evidence of the regenerative changes that precede carcinogenesis in livers damaged by N,N-dimethyl-*p*-aminoazobenzene (17), nor was bile duct proliferation seen. A degree of periportal lymphocytic infiltration was recorded for several animals. Not all kidneys were examined, but the damage in those studied was only slight, and the acute or chronic toxic nephritis found in mice injected with N,N-dimethyl-*p*-aminoazobenzene, or even aminoazobenzene (see below) was never seen.

EXPERIMENTS WITH *p*-AMINOAZOBENZENE

Experimental data.—Only stock mice of mixed colors were used for this series, which was begun in March, 1943. By this time, Miller, Miner, Rusch, and Baumann (15) had shown that hepatic tumors could be induced in rats fed dimethylaminoazobenzene in the following restricted diet:

Crude casein	9 to 12 per cent
Cerelose	80 " 77 " "
Salts	4 " "
Cotton seed oil	5 " "
Cod liver oil	2 " "
Vitab (0.2 gm. per rat per day).	

Cottonseed oil, however, was in very short supply in Britain at this time, and neither cerelose, dextrin, nor starch was available. A partially purified diet was therefore adopted as follows:

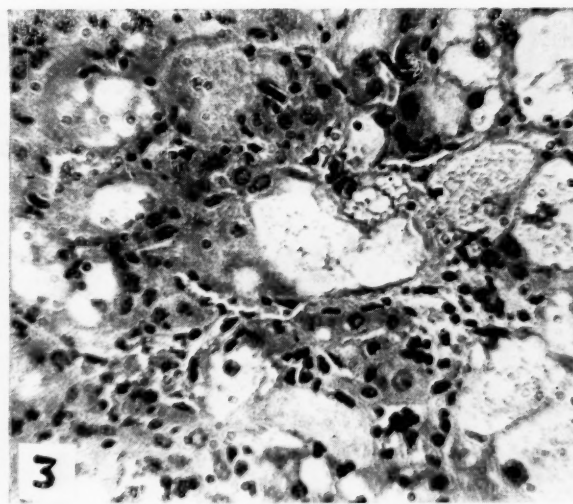
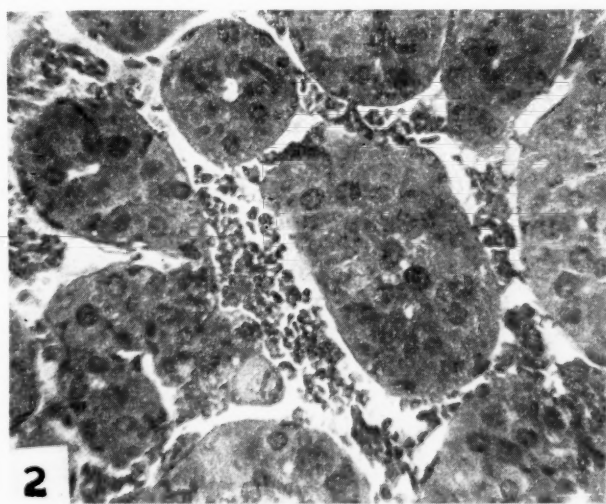
Cascin (Glaxo extracted)	10	per cent
Boiled potatoes	75	" "
Salt mixture (Glaxo, LD6)	4	" "
Yeast (D.C.L. dried, baker's)	2	" "
Arachis oil	8	" "
Cod liver oil	1	" "
	100	" "

The mice were divided into 2 groups, one of which was fed the full diet of rat cake whereas the other received the restricted diet. In this way it was hoped

to discover whether the carcinogenic action of azo dyes in mice is subject to dietary influence or not.

The dye was incorporated in arachis oil, and 0.25 ml. was injected per mouse once a fortnight. A 3 per cent solution was used for the first 10 mice, but as half of them died within 48 days the strength was reduced to 2 per cent for all subsequent injections of the survivors and of other mice started later. Thus the amount injected per fortnight was 5 mgm. per mouse.

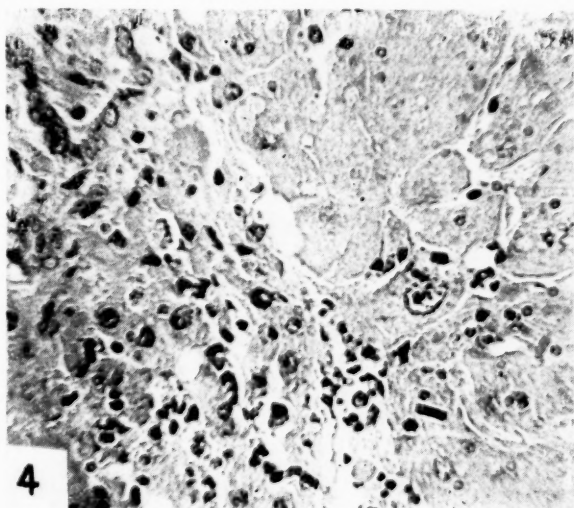
Results.—Of mice receiving the restricted diet, only 8 of 29 survived for more than 100 days; 3 lived more than 300 days, 2 females died at 391 and 431 days respectively, and 1 male lived 626 days. The amounts of dye received by the 3 mice last named were 117.5



Subcutaneous injections of 4'-amino-2,3'-azotoluene in Cba Mice:

FIG. 2.—Embryonic type of liver hyperplasia in male mouse dying at 432 days after receiving 120 mgm. of dye. Mag. $\times 380$.

FIG. 3.—Hepatoma with foamy cell degeneration in female mouse dying at 333 days; total dye, 100 mgm. Mag. $\times 390$.



Subcutaneous injections of 4'-amino-2,3'-azotoluene in Cba Mice:

FIG. 4.—Junction of normal tissue and hepatoma in female mouse dying at 327 days; total dye, 100 mgm. Mag. $\times 410$.

mgm., 140.0 mgm., and 192.5 mgm. respectively; the kidneys of the first 2 showed no gross abnormality, but the male had chronic toxic nephritis. Mice dying earlier usually had some degree of acute toxic nephritis. No tumors were seen in the liver in any mouse; necrosis was frequent, both focal and otherwise, but fatty degeneration was not. The female dying at 431 days had leukemic infiltration of the liver and spleen, a condition seen in several mice dying much earlier. The skin invariably showed cystic spaces at the site of injection, with little reaction; the last survivor had a local foreign body giant cell reaction. In the spleen, the reticuloendothelial cells were usually very numerous and loaded with golden-brown pigment; in some cases the germinal centers or the entire malpighian bodies were degenerated.

Among the 7 mice fed on rat cake that were examined post mortem, 4 had survived 300 days' treatment; 2 males had each received a total of 98 mgm.

of dye, 1 female 113 mgm., and 1 male 120 mgm. Evidence of toxic nephritis was usually present. The skin showed only cystic spaces at the site of injection, and no neoplastic changes were found in the liver. The spleens had pigmented reticuloendothelial cells, but in 2 cases showed a peculiar hyaline degeneration around the malpighian bodies that did not stain for amyloid. Very similar lesions have been described recently by Parsons in mice treated with pentose nucleotides (18).

No unequivocal signs of even early cirrhosis were found in the liver of any mouse on either diet, and it seems safe to say that *p*-aminoazobenzene does not induce cirrhosis in stock mice. Moreover, no liver tumors were found, although only 1 mouse survived

other flank once a fortnight. The same volume and frequency of injection was employed for 4'-amino-2,3'-azotoluene, which was used at a strength of 2 per cent, in arachis oil. Thus 7.5 mgm. of *N,N*-dimethyl-*p*-aminoazobenzene or 5 mgm. 4'-amino-2,3'-azotoluene was injected per mouse on each occasion.

Results.—I. *N,N*-dimethyl-*p*-aminoazobenzene series.—Table I shows (a) the number of mice used in each series that were examined post mortem; (b) the number of these that survived for 250 days or more; and (c) the days of experimentation that passed before any individual was found post mortem to have either sarcoma or a liver tumor (animals with large tumors were sacrificed).

TABLE I: INCIDENCE OF TUMORS IN MICE INJECTED WITH *N,N*-DIMETHYL-*p*-AMINOAZOBENZENE

	Strain	Mixed		Cba		C57 black	
		♂	♀	♂	♀	♂	♀
Full diet	No. mice examined post mortem	9	4	11	none	5	7
	No. surviving 250 days	9	3	8	none	3 *	5
	Sarcoma found at, days	344, 379	none	none	none	none	321
	Liver tumor found at, days	429, 432	438	(511)‡ 515, 552, 556		"	446, 529, 530, 615
Restricted diet	No. mice examined post mortem	5	10	11	4	7	5
	No. surviving 250 days	1	2	6 †	0	0	0
	Sarcoma found at, days	none	none	none	none	none	none
	Liver tumor found at, days	"	382	"	"	"	"

* Survived 443, 470, and 474 days respectively.

† Last died at 426 days.

‡ Nodular hyperplasia and angiomatous cystic spaces.

as long as the rats that developed liver cancer when fed the same dye (11). However, the absence of even proliferation in the 4 mice that survived a year or more suggests that *p*-aminoazobenzene is not likely to prove a carcinogen for mice by the subcutaneous route.

EXPERIMENTS WITH 4'-AMINO-2,3'-AZOTOLUENE AND *N,N*-DIMETHYL-*p*-AMINOAZOBENZENE

Experimental data.—These 2 series were carried out concurrently with the *p*-aminoazobenzene series, but besides stock mice of mixed colors mice of 2 pure strains, Cba and C57 black, were used.

As in the *p*-aminoazobenzene series, each group was divided into 2 subgroups, one receiving a full diet of rat cake, while the other was given the restricted diet described above. As the sexes were kept separate there were thus 4 subgroups of each strain on *N,N*-dimethyl-*p*-aminoazobenzene and, similarly, 4 groups on 4'-amino-2,3'-azotoluene.

The azo dyes were incorporated in arachis oil. *N,N*-dimethyl-*p*-aminoazobenzene was soluble at body temperature to the extent of 3 per cent, and 0.25 ml. of this solution was injected subcutaneously in one or

The following conclusions emerge from these findings:

1. Sarcoma and liver tumor were never found in the same animal.
2. Liver tumors are commoner than sarcomas in mixed and in pure strains.
3. The time required for sarcoma formation was much less than that required for liver tumor formation, both in the mixed strain mice and in C57 black.
4. In the mixed strain mice, tumors were found in 4 out of 8 males surviving more than 250 days, but in only 1 out of 3 females surviving for the same minimum period. In C57 black mice, only the females developed tumors, either sarcoma or liver tumors, although 3 males survived for 433, 470, and 474 days respectively and the livers in all showed pericellular and/or peribulbar cirrhosis.
5. Cba mice seem especially resistant to the induction of subcutaneous tumors, 7 male mice on full diet and 6 on restricted diet living to or beyond the age at which the other strains developed sarcomas, without any sign of reaction at the site of injection.

II. 4'-Amino-2,3'-azotoluene.—Table II records the corresponding data for the 4'-amino-2,3'-azotoluene experiments. The following conclusions may be drawn from a comparison of Tables I and II:

1. The effect on the liver of the compound having its methyl groups linked to carbon is much greater than that of the isomer in which the methyl groups are linked to nitrogen.

2. On the contrary, 4'-amino-2,3'-azotoluene appears to be the weaker sarcogen of the two dyes, though it is not entirely devoid of this power, and the latent period for the one sarcoma found was actually shorter than for those induced by the other dye.

3. The latent period for hepatoma formation is much less in the case of 4'-amino-2,3'-azotoluene: this is well shown in the Cba mice, where there is no overlap at all between the 2 experiments in the times elapsing before liver tumors were found. It is shown just as clearly by the C57 black females and the heterozygous males, but the females of the mixed strain show no difference.

4. Whereas the C57 black mice show a clear-cut sex difference in their susceptibility to N,N-dimethyl-*p*-aminoazobenzene, this is not true for 4'-amino-2,3'-azotoluene, which actually induced

period required for sarcoma development in mice of the other strains, but none of them showed any significant reaction at the site of injection. The lesions in the mice of mixed origin were spindle cell sarcomas; that in the C57 black female mouse was a fibro- and mixed-cell sarcoma.

Liver lesions.—Three males and 5 females of the C57 black strain survived 250 days, but whereas none of the livers of the males showed more than a slight pericellular and/or periportal increase in reticulum and, in 1 mouse, some degree of anisocytosis, the livers of 4 females showed cirrhosis and hepatoma formation, amounting in 1 dying at 530 days to primary liver cell carcinoma. This result demonstrates the pronounced

TABLE II: INCIDENCE OF TUMORS IN MICE INJECTED WITH 4'-AMINO-2,3'-AZOTOLUENE

Strain		Mixed		Cba		C57 black	
		♂	♀	♂	♀	♂	♀
Full diet	No. mice examined post mortem	6	4	6	6	7	8
	No. surviving 250 days	2	4	5	5	5	5
	Sarcoma found at, days	none	none	none	none	none	252
	Liver tumor found at, days	233,	408	259	326	385	278
		384 M	423 M	379	327	403	308
Restricted diet			452	379	333	427	407
			460	432	343	437 M	
			432		500		
	No. mice examined post mortem	8	14	4	16	8	10
	No. surviving 250 days	0	3	1	0	1	0
Restricted diet	Sarcoma found at, days	none	none	none	none	none	none
	Liver tumor found at, days	"	366 M	"	"	515	"
			381 M				
			483				

M signifies that metastases from the primary tumor were found.

hepatic tumors by 515 days in all of 6 males, compared with 3 out of 5 females. The sarcomas induced by either compound were both in female mice.

5. Metastases were found from five 4'-amino-2,3'-azotoluene-tumors, as compared with none in the other experiment (see Fig. 10).

LESIONS IN MICE RECEIVING N,N-DIMETHYL-*p*-AMINOAZOBENZENE

Sarcoma.—Only a very few sarcomas were found in mice injected with N,N-dimethyl-*p*-aminoazobenzene. Law, who also used C57 black mice (12), obtained sarcomas in just over 20 per cent of the mice of this strain. As can be seen from Table I, in these experiments 1 out of 5 female C57 black mice died with a sarcoma at the site of injection after 321 days; the 3 males survived longer than this, but none developed a sarcoma. Among the mice of mixed origin, 2 out of 9 males died at 344 and 379 days respectively, with sarcomas at the site of injection, while none of 3 females developed such a tumor. Several of the male mice of the Cba strain lived much longer than the

sex difference in susceptibility in this strain of mouse to the induction of liver tumors by N,N-dimethyl-*p*-aminoazobenzene; this difference appears to be the same for sarcoma induction, also. But the result here described does not accord with the results either of Law (12) or of Andervont and Edwards (2), who obtained no liver tumors by a similar technic; *i.e.*, subcutaneous injection of an oily solution. However, the difference is probably due to the difference in dosage. Law's mice received a total of 10 mgm., Andervont and Edwards' 45 mgm., whereas the tumor-bearing C57 black mice in the experiments reported here received totals of 172.5, 187.5, 210.0, and 210.0 mgm. respectively. Moreover, Andervont and Edwards killed all their mice at 1 year, whereas hepatoma due to N,N-dimethyl-*p*-aminoazobenzene was not seen before 382 days in any of our groups. The induction of liver tumors was not confined to the C57 black strain, although no female Cba mice survived more than 208 days and showed only anisocytosis of liver cells. Of 14 male Cba mice surviving 250 days, 3 developed hepatomas (after an average period of

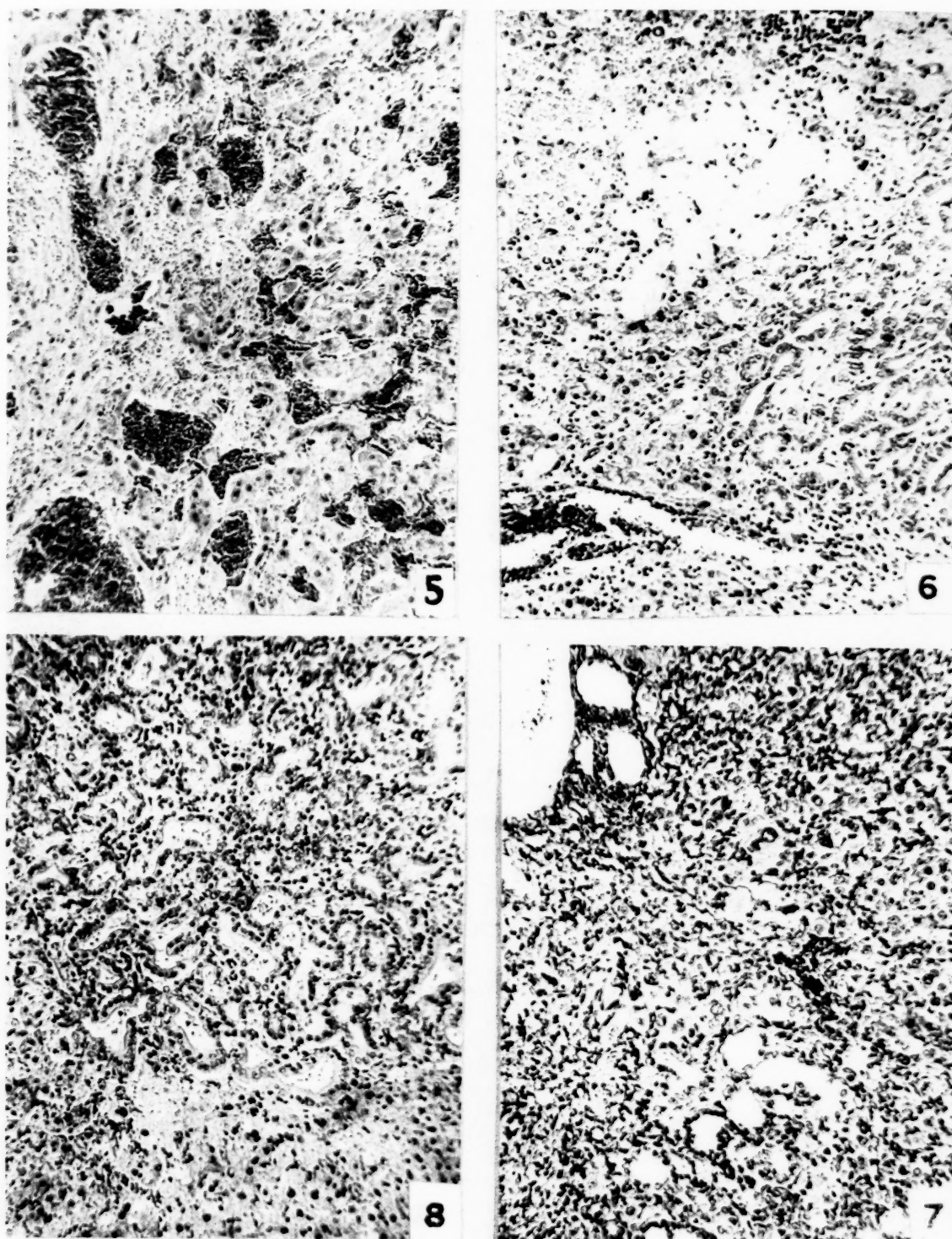


FIG. 5.—Mixed hepatoma and angioma in male Cba mouse dying at 515 days after receiving 232.5 mgm. of *N,N*-dimethyl-*p*-aminoazobenzene by subcutaneous injection. Mag. $\times 100$.

FIGS. 6-8.—Livers of stock mice receiving injections of 4'-amino-2,3'-azotoluene:

FIG. 6.—Male mouse dying at 384 days; total dye, 115 mgm. Extensive bile duct proliferation, and group of pale, xanthoma-like cells. Mag. $\times 170$.

FIG. 7.—Female dying at 84 days; total dye, 30 mgm. Adenomatous type of hepatoma. Mag. $\times 170$.

FIG. 8.—Female dying at 452 days; total dye, 130 mgm. Extensive cholangioma. Mag. $\times 170$.

540 days and total injections of from 232.5 to 247.5 mgm.), and 1 of these had hemangioma mixed with the hepatoma (Fig. 5); a fourth had nodular hyperplasia and hemangiomatous cystic spaces. Others in this group showed anisocytosis and apparent regeneration of liver cells. A fine degree of cirrhosis, either pericellular or perilobular, was a frequent but not essential feature. In the group of mice of mixed origin, both sexes had survivors beyond 250 days and both were prone to liver tumors. Of 10 males and 5 females, 2 of each sex developed hepatoma, the average induction period being 420 days for either

cell sarcoma containing giant cells after a total of 75 mgm. of dye had been injected, at 252 days.

Liver lesions.—Few mice of any group surviving 250 days failed to develop liver tumors. A fine, usually pericellular, increase of reticulum appeared early in the livers of mice of all groups and on either diet; in some mice dying later it was considerable, in others absent. Cirrhosis, in fact, was a common but by no means invariable feature, and was not even always present in mice dying with liver tumors.

All except 1 male of the mice of mixed origin surviving 250 days, and also 1 male dying at 233 days,

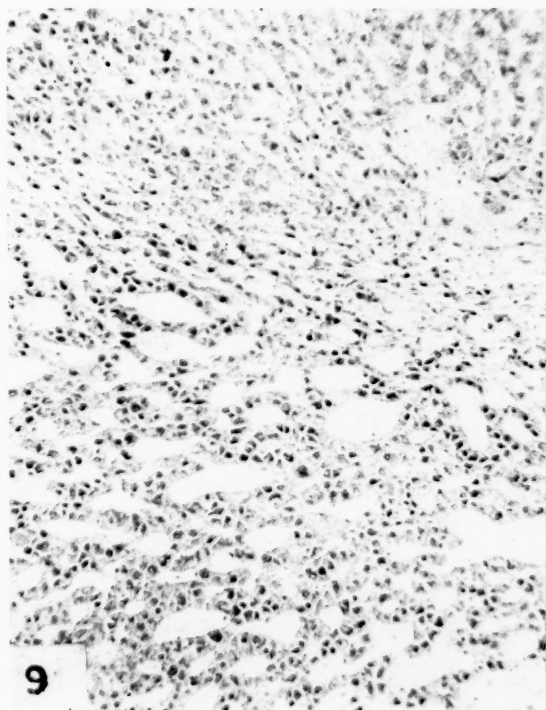


FIG. 9.—Cavernous angioma in liver of a control C57 black male mouse dying at 497 days. Mag. $\times 90$.

FIG. 10.—Secondary liver cell carcinoma in a perirenal vein in a female stock mouse dying at 381 days; total dye (4'-amino-2,3'-azotoluene), 115 mgm. Mag. $\times 170$.

sex. In all cases the amount of dye injected totalled 187.5 mgm. Cirrhosis, pericellular and/or perilobular, was found in nearly all these mice, but in no case was the hepatoma considered malignant, as no metastases were found.

Other sites.—Toxic nephritis, either acute or chronic, was a common feature in all groups of mice receiving this dye. One male mouse of mixed origin, dying at 432 days, had a lung adenoma.

LESIONS IN MICE RECEIVING 4'-AMINO-2,3'-AZOTOLUENE

Sarcomas.—No sarcomas were found in any of the mice of mixed origin or of the Cba strain. Male C57 black mice likewise failed to develop this type of lesion, but 1 female of this strain developed a spindle

developed liver tumors. One female, which received the restricted diet and died at 366 days, had an anaplastic tumor of the connective tissue with considerable bile duct proliferation and a generalized low-grade hepatomatosis; lymphomatous tumor deposits were found in the spleen, lung, kidney, and submaxillary gland. Of the remaining 8 mice, 3 had secondary deposits of primary liver cell tumor (Fig. 10), and the others had varying degrees of hepatomatosis. A very interesting feature of these mice was the presence of bile duct proliferation. This lesion commonly follows administration of azo dyes, especially N,N-dimethyl-*p*-aminoazobenzene, to rats (6, 17), but was reported by Law only for dba mice (12), and not at all by Andervont and his associates (14). Proliferation of

the bile ducts was seen in both sexes (Figs. 6 to 8) and amounted to cholangioma in 1 female dying at 452 days after 130 mgm. of the dye had been injected (Fig. 8); in no instance was metastasis found, but neoplastic bile ducts merged into neoplastic liver cells with no sharp boundary.

Only 1 Cba mouse receiving the restricted diet survived more than 250 days and its liver exhibited only anisocytosis and a macroscopic, multilocular cyst protruding above the liver surface and filled with clear fluid. Such cysts were seen in 2 male Cba mice fed a full diet and injected with the same dye. Much larger cysts, identical in appearance, have frequently been seen here in the livers of Wistar rats fed N,N-dimethyl-*p*-aminoazobenzene in either the restricted diet described in this paper or in that described as "low protein" by Miller and his group (15); they were also associated with notable cholangiomatosis and were almost certainly cystic bile ducts that had pushed up under the capsule. The same is probably true in these Cba mice, as moderate bile duct proliferation was seen in several with or without the macroscopic cysts. Of the 5 male and 5 female mice fed rat cake and surviving for 250 days, all the males and 4 of the females developed hepatomas but no secondaries were found. The type of hepatoma varied somewhat from a simple type illustrated in Fig. 4 to a foamy cell type (Fig. 3), or a type recalling embryonic growth (Fig. 2); moreover, the tumors tended to be angiomatous. Increase in reticulum tended to be perilobular rather than pericellular but, where present at all, it was never advanced.

No female and only 1 male C57 black mouse receiving the restricted diet survived more than 250 days. The male died at 515 days with definite hepatoma formation; no secondaries were seen, but there was a lymphosarcoma in the retroperitoneal tissues that had invaded the pancreas. Three of 5 female mice of this strain receiving a full diet died with obvious hepatomas associated with a pericellular increase in reticulum; in the case of the mouse dying at 407 days, the hepatoma was mixed with hemangiomatous cysts. All 5 male mice surviving 250 days on the full diet died with hepatomas; 1, dying at 427 days, had a very large, hemorrhagic liver cell carcinoma, and another, dying at 437 days, had secondary deposits of liver cell carcinoma in 1 kidney and the corresponding ureter. The last male, dying at 500 days, had angioma mixed with hepatoma in the liver, and also a hemangioendothelioma behind the left kidney. Pericellular cirrhosis was present in all these livers, but bile duct proliferation was not seen.

Other sites.—Acute to chronic toxic nephritis was commonly found in the mice of all strains. One female of mixed origin, dying at 366 days, had adenoma of the lung; another, dying at 423 days, had secondary

liver cell carcinoma and also hemangioendothelioma in the lung.

THE INFLUENCE OF THE RESTRICTED DIET

The restricted diet proved rather unsatisfactory, relatively few mice surviving more than 250 days. This is also true for control mice that were fed this diet but given no injections. Toxic nephritis was a common finding in all groups on either dye on either diet, but necrosis of the liver was commoner in mice receiving the restricted diet, and the earlier deaths were probably due to a deficiency in the diet that permitted this type of lesion. In any event, there is no evidence that this particular restricted diet promoted the production of liver tumors.

CONTROL MICE ON THE RESTRICTED DIET

Stock mice as well as those of the Cba and C57 black strains were maintained on the restricted diet as controls. Of 5 male and 5 female stock mice coming to autopsy, 3 males died at 157 days with abscesses in the cecum and septic lesions in the liver and stomach. Five out of 6 dying between 210 and 223 days showed some degree of subacute toxic nephritis, but the last mouse, a male, dying at 342 days, showed no abnormality of the kidney nor of the stomach, liver, or spleen. The livers were generally normal; 3 showed congestion. Stomachs were normal except that of 1 male mouse, dying at 214 days, which showed extensive hyperkeratosis and papillomatosis, one papilloma in the fundus being visible to the naked eye.

Only 2 male Cba mice came to autopsy. The stomachs were normal in both. The one dying at 153 days had a normal liver, and only cloudy swelling in the kidney; the other, dying at 252 days, had normal kidneys; some liver cells showed fatty degeneration, and the spleen contained prominent megakaryocytes.

The C57 black control mice were more interesting. Seven were examined post mortem; 3 males died before 100 days, and 2 of these, dying at 84 days, showed a fine, pericellular cirrhosis. The stomachs and kidneys of these 3 mice were normal. No abnormality of the stomach was seen in the other 4, and it appears that the restricted diet did not induce stomach lesions in either Cba or C57 black mice; the lesions seen in 2 out of 9 stock mice appear to indicate some difference in reaction of the squamous epithelium of these mice, but one C57 black mouse receiving injections of N,N-dimethyl-*p*-aminoazobenzene, showed a definite multiple papilloma in the forestomach (Fig. 11). Kidney lesions usually did not exceed cloudy swelling; 1 female, dying after 482 days, had granular debris in the tubules and cystic dilation of the first convoluted tubules. The latter mouse also showed collections of

polymorphonuclear leukocytes in the liver, and presumably had some sort of infection.

Two C57 black mice showed benign spontaneous liver tumors. A male, dying at 456 days, had a cavernous angioma that caused a nodular appearance and led to hemorrhage under Glisson's capsule, but the growth was very orderly (Fig. 9). The other, a female dying at 523 days, had hepatoma in all lobes; gross examination showed nodules of fleshy, vascular tissue a little paler than the normal liver, while the microscopic picture was that of well differentiated, vascular hepatomatous masses with fatty degeneration in many cells. An interesting feature of the hyperplastic nodular zone was the absence of the fibrous capsule from all the blood vessels, which were not arranged in any normal pattern. Little, Murray, and Cloudman (13) reported 5 liver tumors in a total of 875 C57 black mice, of which 2 were carcinomas (in breeding fe-

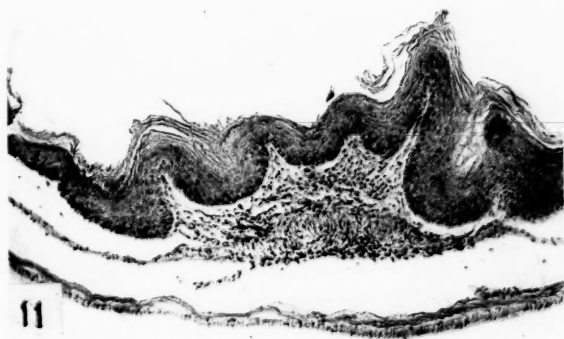


FIG. 11.—Localized papilloma in forestomach of male C57 black mouse dying at 60 days; 30 mgm. N,N-dimethyl-*p*-aminoazobenzene injected subcutaneously; fed restricted diet described in text. Mag. $\times 64$.

males) and 3 were adenomas (in males). None of these animals died earlier than 542 days. As no illustrations were given, nor any description of the tumors, it is impossible to compare our results with those of Little and his associates. These hepatic lesions differed both macroscopically and microscopically from any seen in the livers of mice receiving azo dye injections, which leads us to believe that all the tumors reported in this paper were induced by the azo dyes administered and were not spontaneous.

SUMMARY AND CONCLUSIONS

1. Stock mice injected subcutaneously with 2'-amino-4,5'-azotoluene in olive oil solution, up to 472 days and a total dosage of 67.5 mgm., developed no neoplastic lesions.

2. Similar mice injected subcutaneously with *p*-aminoazobenzene in arachis oil solution, up to 626 days with a total dosage of 192.5 mgm., developed no tumors at any site, either on an adequate diet or on a diet restricted in protein and probably in riboflavin.

3. 4'-Amino-2,3'-azotoluene and N,N-dimethyl-*p*-aminoazobenzene have been injected subcutaneously in arachis oil solution into stock mice, Cba mice, and C57 black mice of both sexes. Hepatoma was induced with either dye in mice of either sex of all three genetic types (except male stock mice receiving the latter dye). Sarcoma at the site of injection was rare in stock and C57 black mice, and was never seen in Cba mice. Lung adenoma was found in only 1 female stock mouse. Hemangioendothelioma was found in a few stock and C57 black mice; simple hemangioma also was found.

4. In mice of mixed origin and also in mice of the Cba and C57 black strains, 4'-amino-2,3'-azotoluene proved much more carcinogenic than N,N-dimethyl-*p*-aminoazobenzene for the liver, when administered in oily solution by the subcutaneous route.

5. No sex difference in susceptibility was observed either in stock mice or in Cba mice with these latter dyes, or in C57 black mice with 4'-amino-2,3'-azotoluene; liver tumors were obtained in female C57 black mice, and not in males, with N,N-dimethyl-*p*-aminoazobenzene.

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Studies in Carcinogenesis with Azo Compounds

II. The Action of Azo Compounds in Mice, and the Bearing Thereof on Theories of Azo Dye Carcinogenesis*

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INTRODUCTION.

INVESTIGATIONS WITH AZO COMPOUNDS:

A. LIVER LESIONS (SEE TABLE I)

1. *p*-Aminoazobenzene (AAB)
2. 2'-Amino-4,5'-azotoluene (*p*AAT)
3. 2,3'-Azotoluene (AT)
4. Azonaphthalenes (AN)
5. 4'-Hydroxy-2,3'-azotoluene (*o*HAT)
6. N,N-Dimethyl-*p*-aminoazobenzene (DAB)
7. 4'-Amino-2,3'-azotoluene (*o*AAT)

B. TUMORS AT THE SITE OF INJECTION (SEE TABLE II)

C. LUNG TUMORS (SEE TABLE III)

D. ENDOTHELIOMAS (SEE TABLE IV)

E. LIVER LESIONS OTHER THAN LIVER CELL TUMORS

STRAIN SUSCEPTIBILITY.

THEORIES OF THE MECHANISM OF TUMOR INDUCTION BY AZO COMPOUNDS

INTRODUCTION

The results of earlier investigations of the carcinogenic action of azo dyes in rats were summarized by Kinosita in 1937 and 1940 (22, 23), and by Hartwell in 1941 (17). Since then much work has been done involving various types of controlled, restricted diets and a theory has been evolved (19) to account for the activity of certain dyes and the inactivity of others. A short review of this work appeared in a recent paper by Miller and Baumann (29), who criticized the theory on the basis of their own experimental findings. A considerable amount of work on mice has been carried out with azo compounds since the earlier reviews appeared, but no attempt has been made to examine it critically and to determine its bearing on the "split product" theory of carcinogenesis.

In this paper, in a series of tables, there has been

collated the information available in the literature regarding the production of neoplastic growths in mice by such azo compounds as have been shown to have any effect by any route. It will be seen that a number of pure strains have been used by various workers, and that these provide a fair degree of checking upon each other. 4'-Amino-2,3'-azotoluene has usually been employed, but investigations have also been made with N,N-dimethyl-*p*-aminoazobenzene by four groups of workers other than the present author, with 2,3'-azotoluene by two groups of workers, and 4'-hydroxy-2,3'-azotoluene and 1,1'- and 2,2'-azonaphthalenes in one case each, only. These azo compounds have been fed, painted on the skin, or injected subcutaneously; for the latter route either the solid or an oily solution has been used, leading to some significant differences in response. While liver tumors have been the predominating interest, growths at the site of injection, pulmonary neoplasms (other than metastases), and endotheliomas of various types and at various sites have been observed by several workers. No tumors at the site of painting or in the alimentary tract, with two exceptions (10, 25), have been reported. The data are discussed in the text for each azo compound and also from the points of view of the lesions induced and the response by any particular strain of mouse that has been used.

Certain clear-cut facts emerge from the data now available and their bearing on the "split product" theory and on the older "rearrangement" theory of Cook and his group (10), recently extended by Elson and his co-workers (12, 13), is discussed in a later section.

INVESTIGATIONS WITH AZO COMPOUNDS

A. LIVER LESIONS (SEE TABLE I)

1. *p*-Aminoazobenzene (abbreviation: AAB).—Yoshida reported (49) having injected mice subcutaneously with a 10 per cent solution of AAB in olive oil, but none of them survived more than 23 days and

* Because of the difficulties of international communication the author has not read proof of this article.

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hence no data were provided on the carcinogenicity of this dye for mice. The experiments reported in the preceding paper (25) included 2 mice surviving about 400 days and 1 that survived 626 days under experimentation. No tumors were seen in any of these mice, but it has to be borne in mind that 500 days were required to induce liver tumors in rats fed this dye at a high level (24) and the possibility therefore remains that tumors might arise in mice fed AAB or receiving it by subcutaneous injection for a very long time. Against this is the fact that, although necrosis and other signs of damage were frequently found in the livers of these mice, neither regenerative hyperplasia nor cirrhosis was observed; these latter lesions, or at least regenerative hyperplasia, seem to be an essential premalignant reaction to other azo compounds.

The only other organ suffering consistently was the kidney, in which some degree of toxic nephritis was usually found. Renal changes were reported by Maruya in rats fed this azo dye, or 2,4'-diaminoazobenzene, or even the simple parent compound, azobenzene (28).

2. 2'-Amino-4,5'-azotoluene (abbreviation: pAAT).—This azo dye was reported by Sasaki and Yoshida (41) to have no carcinogenic action when fed to rats up to 476 days. It has also been described as 5'-amino-2,2'-azotoluene (41) and 4'-amino-2,2'-azotoluene (11), but Hartwell (17) accepts the formulation of Miura (34), and this is certainly the compound used by Kirby (25). The latter found no tumors in stock mice injected subcutaneously with an olive-oil solution of this dye up to 472 days; necrosis of the liver was frequent, but cirrhosis and the premalignant regenerative

hyperplasia were not seen. Moreover, pAAT did not apparently damage the kidneys.

Tests by other routes do not appear to have been carried out, and it is just possible that this azo dye might prove to be a weak carcinogen if presented suitably and long enough.

3. 2,3'-Azotoluene (abbreviation: AA).—This azo compound and the following two are of special interest, as they contain no amino group and therefore cannot be broken down to yield a diamine of the type required for the "split product" theory, although they all could undergo a benzidine type of rearrangement. AT has been reported to cause bladder papilloma when fed to rats in a rice diet (39), a finding that has been confirmed by Cook (9), who also investigated the effect on mice receiving the compound orally or by subcutaneous injection; the mice developed no significant lesion.

Two other investigations with AT have been carried out in mice. Seligman and Shear (42) injected the pure compound, which is an oil, subcutaneously into female mice of strain A, but even after 18 months no tumors had developed; it will be seen from Table I that strain A mice of either sex are easily susceptible to tumor induction, both in lung and in liver, by the *p*-amino derivative of AT, namely, 4'-amino-2,3'-azotoluene. Law (26) gave 3 subcutaneous injections of AT, 5 mgm. total, in olive oil during 2 months; he also reports introducing a 5 mgm. pellet at 4 months of age, but as AT is a liquid it is not clear whether or not he gave a fourth dose in the case of this compound. His dba mice developed neither sarcoma nor liver tumor; but among 20 C57 black mice 2 developed

KEY TO TABLES I TO IV

pAAB — *p*-aminoazobenzene.
pAAT — 2'-amino-4,5'-azotoluene.
oAAT — 4'-amino-2,3'-azotoluene.
BY — N,N-dimethyl-*p*-aminoazobenzene.
AT — 2,3'-azotoluene.
1,1'-AN — 1,1'-azonaphthalene.
2,2'-AN — 2,2'-azonaphthalene.
pHAT — *p*-hydroxyazotoluene.

1. Hepatomas unless otherwise indicated.
2. Adenoma; annular cirrhosis.
3. After 340 days.
4. Unspecified.
5. Focal necrosis; fatty degeneration.
6. After 11 months.
7. "Characteristic changes . . . which precede malignancy."
8. Law gives no figures for survival of mice not bearing tumors in any of his groups.
9. After 11 months; 3 mice had received liver supplements and 2 of these had normal livers, but all had sarcomas.
10. Mice bearing tumors are in all cases expressed as a fraction of the total mice surviving 250 days or longer.
11. Hemangioendothelioma, unless otherwise stated.
12. Hartwell (17) refers to lung tumors, but quotes no figures.

13. After 46 weeks.
14. After 42 weeks.
15. After 50 weeks.
16. After 44 weeks.
17. After 32 weeks.
18. After 38 weeks.
19. At 52 weeks.
20. At 42 weeks.
21. 2 at 41 weeks; 1 at 50 weeks.
22. At 41st week.
23. 1 at 42 weeks; 1 at 52 weeks.
24. 1 at 51 weeks; 1 at 52 weeks.
25. At 344 and 379 days respectively.
26. At 252 days.
27. At 321 days.
28. Adenoma; 2 other female mice had secondary liver cell carcinoma.
29. 1 reticuloendothelioma; 2 hemangioendothelioma.
30. 1 hemangioendothelioma behind left kidney; 1 lymphoma, invading pancreas, in retroperitoneal tissues.
31. Reticuloendothelioma.
32. Nearly all cholangiomas.
33. 4 females had cirrhotic livers.

TABLE I: EFFECT OF AZO COMPOUNDS ON THE LIVER IN MICE

Author	Azo compound	Solvent	Dose	Route	Experimental period	Incidence of liver lesions ¹												
						Mixed	M	A	P.-B.	C	I	C3H	Y	dba	Cba	C57 black		
Smith (49)	oAAT	Olive oil 10%		SubQ		Liver ² changes												
Williams (37)	oAAT		0.3 mgm. per gm. diet	Per os	400 days	6/7 ³												
Smith and Lacey (35)	BY			Per os		Liver ⁴ changes												
Wood and Jones (8)	oAAT	Benzene 0.3%	About 4.5 mgm.	Skin painting	104 days	Liver ⁵ changes												
Lee (43)	oAAT	Solid used	7x10 mgm.	SubQ	14 mo.		13/16 ⁶											
Krenskaya (5)	oAAT	Olive oil	0.5 gm. total	Per os	8 mo.	14/30												
		Benzene	0.1 gm. total	Skin painting	8 mo.	22/40			?/23									
		Sunflower seed oil	0.01 gm. total	SubQ	8 mo. 1 yr.	2/17			?/19									
Wasson, Jacobi, and Ruseh (7)	oAAT		0.5 mgm. per gm. diet	Per os	400 days					16/16 ⁷								
Wasson (1)	oAAT	Solid used	11x10 mgm.	SubQ	1 yr.			♂ 7/8		♀ 14/14	♀ 6/9	♀ 10/10	♂ 9/9	♂ 2/7	♀ 3/6			
McHewitt, Ginnaway, and Ginnaway (10)	1, 1'—AN	Olive oil or butter	5 mgm. per wk.	Per os	587 days	4/22 ³²												
		Benzene 0.6%		Skin painting	549 days	0/4												
	2, 2'—AN	Sesame oil	?x5 mgm.	SubQ	566 days	2/16 ³²												
		Olive oil or butter	5 mgm. per wk.	Per os	493 days	28/30 ³²												
		Benzene 0.6%		Skin painting	828 days	5/5 ³²												
		Sesame oil	?x5 mgm.	SubQ	540 days	14/23 ³²												
McHewitt (10)	oAAT	Olive oil solid used	10 mgm. total	SubQ	654 days										7/30 ⁸		1/30	
	BY	"	"	"	at least 581 days										1/30		0/29	
	oHAT	"	"	"	at least 629 days										1/24		1/30	
	AT	"	"	"	at least 639 days										0/22		2/20	
Wasson and Stewart (42)	AT	Liquid used	0.05 ml.	SubQ	18 mo.			♀ 0/20										
Wasson and Stewart (42)	BY	Solid used	7x10 mgm.	SubQ	15 mo.			0/10							♂ 0/10			
Wasson and Muliken (47)	oAAT	Corn oil	at least 130 mgm.	SubQ	over 1 yr.					6/10 ⁹								
Wasson, Grady, and Edwards (5)	oAAT	Solid used	100 mgm.	SubQ	1 yr.			♂ 5/11	♀ 11/11	♂ 1/12	♀ 12/12	♂ 5/23				♂ 3/34	♀ 13/13	
Wasson and Edwards (3)	oAAT	Olive oil 2%	45 mgm.	SubQ	1 yr.			♀ 7/7		♂ 0/29	♀ 15/20	♂ 0/9	♀ 1/8			♂ 0/20	♀ 16/21	
	BY	"	"	"	"			none		none						none		
Wasson and Edwards (4)	oAAT	Crystals used	10 mgm.	SubQ	52 wk.			♀ 6/20										
			20 mgm.					6/20										
			30 mgm.					8/20										
			40 mgm.					10/20										
			50 mgm.					11/20										
			60 mgm.					13/20										
Wasson, White, and Edwards (6)	oAAT		Max. 220 mgm.	Per os	223 days					♂ 8/29	♀ 24/31							
	BY		About 300 mgm.	"	270 days					0/8	1/6 ³³							
Wasson (25)	pAAT	Olive oil 1 or 2%	67.5 mgm. total	SubQ	472 days	0/11												
	pAAB	Arachis oil 2%	192.5 mgm. total	"	626 days	0/9												
	oAAT	"	Up to 130 mgm.	"	515 days	♂ 2/3	♀ 7/7								♂ 5/6	♀ 4/5	♂ 6/6	♀ 3/5
	BY	Arachis oil 3%	Up to 247.5 mgm.	"	615 days	♂ 2/9	♀ 2/5								♂ 3/14	♀ 0/0	♂ 0/3	♀ 4/5

hepatoma at 585 and 639 days respectively, and 5 developed sarcomas at the site of injection at a mean age of 361 days. Spontaneous liver tumors in C57 black mice were reported by Little, Murray, and Cloudman (27) after 540 days, and were seen by Kirby (25) in a male dying at 456 days and a female dying at 523 days. Hence the liver tumors seen by Law in mice of this strain receiving AT may have been spontaneous. But this would hardly apply to the sarcomas, which are rare at any age. Andervont and Edwards (3) concluded that sarcoma arose more easily when 4'-amino-2,3'-azotoluene was injected in oily solution than as a solid. Law's positive results in C57 black mice and Seligman and Shear's negative results in strain A mice may therefore be due to difference in strain, or to the use of an oily vehicle by Law, or to both differences. It seems clear that AT is not carcinogenic for the liver of the mouse.

4. (a) *2,2'-Azonaphthalene* (abbreviation: 2,2'-AN).—The only investigations with azonaphthalenes in mice were carried out by Cook, Hewett, Kennaway, and Kennaway (10), who found definite hepatic lesions following the administration of 2,2'-AN either by feeding, painting or subcutaneous injection. These lesions were almost always cholangiomatous, with only an occasional hepatoma; this is in sharp contrast with the picture usually seen in the livers of mice receiving *N,N*-dimethyl-*p*-aminoazobenzene or 4'-amino-2,3'-azotoluene, which rarely induce cholangioma (25), but is in harmony with the histology of liver lesions induced by the "benzidine-type rearrangement" product of 2,2'-AN, namely, 2,2'-diamino-1,1'-dinaphthyl (10), and by the de-amination product of the latter, namely, 3,4,5,6-dibenzcarbazole (2, 8, 45). The possible significance of the type of liver lesion associated with these compounds is discussed in a later section of this paper.

Tumors of the lung were also seen in mice receiving 2,2'-AN, including some very large adenomas; whether or not this was after administration by all three routes is not mentioned.

(b) *1,1'-Azonaphthalene* (abbreviation: 1,1'-AN).—This isomer had a slight action on the liver when fed or injected; the few survivors after painting showed no liver lesions. The type of liver tumor was cholangioma in 5 out of the 6 mice affected; the sixth mouse showed a doubtful hepatoma. A squamous cell carcinoma was found in the stomach of 1 mouse that had been fed 1,1'-AN. Another, injected subcutaneously, had a malignant spindle cell and giant cell sarcoma at the site of injection after 441 days; numerous metastases were found in the peritoneal cavity.

5. *4'-Hydroxy-2,3'-azotoluene* (abbreviation: oHAT).—This compound, unlike the preceding two, is substituted in one *para*-position, but the substituent is a

hydroxy and not an amino group; hence it could not yield a *p*-diamine by reductive fission. The only experimental work reported with oHAT was carried out by Law (26), who injected a total of 5 mgm. in olive oil solution followed by a 5 mgm. pellet of the solid azo compound, all subcutaneously in the same zone. Slight activity against the liver was indicated by the finding of hepatoma at 629 days in a mouse of dba strain, in which spontaneous hepatoma is very rare; a similar lesion in a C57 black mouse at 604 days may have been spontaneous. No sarcomas were found in dba mice, but 11 out of 30 C57 black mice developed fibrosarcoma at the site of injection at a mean age of 350 days; *i.e.*, 290 days after the first injection. In Law's experiments this is almost as high an incidence as he obtained with the 4'-amino-derivative of AT, but the latent period was about one-third longer. Law observed no tumors in the bladder, alimentary tract, or lung, and no hemangioendothelioma.

6. *N,N*-Dimethyl-*p*-aminoazobenzene (abbreviation: DAB).—Five groups of workers have investigated the effect of this dye in mice. The earliest report, that by Mizuta and Maruya (35), records "changes in the liver" according to Hartwell (17); the dye was fed in the food, but details of dosage or of the duration of the experiment are not available (17).

Law (26) administered DAB to mice of the dba and of the C57 black strains, 5 mgm. in olive oil followed by a 5 mgm. pellet, subcutaneously. Liver changes were apparently only minor, since no tumors of this organ were seen in C57 black mice and only 1 dba mouse, dying at 581 days, developed hepatoma. Out of 106 dba mice injected by Law with one or other of 4 azo compounds, only 1 developed fibrosarcoma at the site of injection and this, dying at 476 days, had received a total of 10 mgm. of DAB. On the other hand, while 20.7 per cent of the C57 black mice treated with DAB developed fibrosarcoma at the site of injection, this was only approximately half the incidence Law obtained in this strain by injecting oHAT or oAAT. Law's results indicate that DAB is a stronger sarcogen than carcinogen.

According to Hartwell (17) and to Andervont and Edwards (3), Shear and Stewart injected up to 70 mgm. of DAB in the form of crystals into mice of the dba and A strains, without eliciting any tumors at any site up to 15 months after the first implantation. The period employed was shorter than that of Law (26), whose dba mice yielded no tumors until more than 15 months had elapsed. Moreover, crystals were used, whereas Law injected first an oily solution, which probably favored sarcogenesis.

Andervont and Edwards (3) injected subcutaneously a total of 45 mgm. of DAB dissolved in olive oil into mice of both sexes of strains A, C, and C57 black.

In spite of the increased dose, compared with that of Law, none of these mice showed even microscopic liver changes. No tumors were found at the site of injection in strain A or strain C mice, but 2 females of the C57 black strain that died during the 41st week of the experiment (after about 280 days) had fibrosarcomas related to the site of injection. There was therefore further evidence that DAB can act as a sarcogen in at least one strain of mouse, but no evidence that it can act as a carcinogen for the liver or other tissues.

This noncarcinogenicity of DAB for mouse liver stood in sharp contrast with the powerful carcinogenic action it is known to have on the liver of rats. In the latter species, however, administration has almost invariably been *per os*. Special interest, therefore, lies in the experiments of Andervont, White, and Edwards (6), who fed DAB to strain C mice of both sexes at the usual level of 0.06 per cent in a low-protein:high-fat diet containing 0.5 per cent cystine; all these dietary modifications are known to favor DAB carcinogenesis in rat liver (33, 38, 48). They obtained no liver lesions in the 8 male mice that survived 310 days and appear to have consumed at least 300 mgm. of DAB each. Of 6 female mice, which presumably would consume less food and therefore less dye than the males, 4 had cirrhotic livers and 1 had 3 hepatomas. Experiments with restricted diets in other animals (16) suggest that the cirrhosis might have been entirely due to the unbalanced nature of the diet and/or to restricted intake consequent upon the unpalatable dye, but the presence of hepatomas in 1 mouse liver indicated that DAB might have a definite carcinogenic effect, at least when administered orally. Unfortunately, only strain C mice were used in these experiments and this strain has not been employed by other workers.

That DAB can produce severe and neoplastic lesions in the livers of mice has been shown by Kirby (25), who injected the dye, 7.5 mgm. in arachis oil, once a fortnight, subcutaneously into stock mice of mixed genetic constitution and into mice of the Cba and C57 black strains. Among the stock mice, 2 out of 10 males and 2 out of 5 females (surviving 250 days) developed hepatoma; these 4 animals had each received a total of 187.5 mgm. of DAB, and the average latent period was 420 days. Only male Cba mice survived more than 208 days, but 3 out of 14 died with definite hepatomas, 1 having hemangioma mixed with hepatoma; total dye received by these 3 mice ranged from 232.5 to 247.5 mgm., and the average induction period was 540 days. The males of the C57 black strain developed no liver tumors, although an early increase of reticulum was usually present. Four out of 5 females surviving 250 days developed both cirrhosis and hepatoma;

in 1 dying at 530 days the liver-cell tumor was histologically malignant. The amounts of dye administered to these 4 mice were 172.5, 187.5, 210.0, and 210.0 mgm. respectively. Hence it is clear that the livers of all 3 types of mouse are susceptible to DAB given by the subcutaneous route. But in view of the quantities of dye administered in these experiments and, moreover, the duration of the experiments, it is not incomprehensible that positive results should have been obtained when Law and likewise Andervont and his associates found no liver lesions when using the same route of presentation. Kirby also found sarcomas at the site of injection of DAB (see section 3 of this paper).

The cancer-producing activity of DAB is clear for the subcutaneous tissues from the work of Law, of Andervont and his co-workers, and of Kirby, but it is not great and some strains, notably Cba, A, and C, seem to be entirely resistant. The action of DAB on liver seems to be definite also; here again it is relatively weak and in only one instance (a female C57 black mouse) was the liver lesion considered to be definitely malignant; no metastases have been reported. In C57 black mice, and possibly in C strain mice also, the females appear to be more susceptible than the males, but this is doubtful for stock mice of mixed origin. Kirby also reports that toxic nephritis was a common feature in all his mice receiving DAB (25).

7. 4'-Amino-2,3'-azotoluene (abbreviation: oAAT).—By far the largest bulk of information on the action of an azo compound in mice concerns oAAT. It begins with the early observation of Yoshida (49) that annular cirrhosis and adenoma were present in mice (presumably of mixed origin) that had been injected with a 10 per cent olive oil solution of this dye; the total dose administered and the duration of the experiment are not available. Three years later Nishiyama (37) found hepatoma in 90 per cent of mice, also probably of mixed origin, fed the dye at a level of 0.03 per cent up to 400 days. The third normal route of presentation, namely, painting, was employed by Boyland and Brues (8), who used a 0.3 per cent solution in benzene on stock mice and mice of the Simpson strain. Out of 20 mice, 4 survived 95 to 104 days and received about 4.5 mgm. of dye; 3 had focal necroses, and 1 degenerative changes in the liver, but none showed any hyperplastic lesion.

In the same year Shear (43) reported liver carcinoma in 13 out of 16 mice injected with crystals of oAAT, totalling 70 mgm., and surviving 11 to 14 months; whether any of these were in strain M (leaden) mice is not clear, but most of them must have been in strain A mice, although the sexes are not reported separately. Boyland and Brues' negative results were thus shown to be probably due to the insuffi-

cient duration of the experiment. This was confirmed by results that began to appear 2 years later.

Early in 1939 Baumann, Jacobi, and Rusch (7) reported "changes which precede malignancy" in all of 16 strain C mice surviving 8 months on various diets containing 0.05 per cent of *o*AAT; no differentiation was made between the sexes.

According to Hartwell, Morosenskaya (36) painted stock mice with a benzene solution of *o*AAT, administering not more than 0.1 mgm. in the course of 7 to 8 months, and obtained liver tumors of an unspecified nature in 22 out of 40 mice. Morosenskaya found liver tumors in 14 out of 30 mice fed a total of 0.5 mgm. of *o*AAT in olive oil during 7 to 8 months. He also obtained similar lesions in 2 out of 17 stock mice injected with as little as 10 mgm. of the dye in sunflower seed oil and surviving 7 to 8 months. Moreover, this worker employed all three routes to administer *o*AAT to mice of the P.-B. strain, which led in each case to liver tumors in an unspecified proportion of animals. Hence the capacity of this dye to cause hypertrophic lesions of the liver in mice, even in very small doses if given sufficient time, was clearly demonstrated. Before the end of the year Andervont (1) reported results obtained by the implantation of crystals into mice of 5 strains. Hepatoma in 7 out of 8 males of strain A confirmed Shear's findings. Similarly, all of 9 C3H males showed liver tumors, as did all of 14 C females. However, in strain I the incidence among males was only 66 per cent, compared with 100 per cent for females; in strain Y the figure for males was 28 per cent and for females 50 per cent. Thus there came to light here for the first time the difference in susceptibility between the two sexes in certain strains that was to be more clearly revealed in later studies from the same laboratory.

After an interval of nearly 2 years Law (26) reported hepatoma in 7 out of 30 dba mice after 434 days and in 1 out of 30 C57 black mice at 465 days, after subcutaneous injections of *o*AAT in olive oil followed by pellets of the dye. The next year Turner and Mulliken (47) found a 60 per cent incidence of liver lesions after 11 months in 10 strain C mice injected subcutaneously with the dye dissolved in corn oil. Law administered 10 mgm. in all per mouse, while Turner and Mulliken gave at least 130 mgm. Neither group referred to any sex difference in incidence, although Law states that he used "equal numbers of . . . both sexes . . . in each experiment." Meanwhile, Andervont, Grady, and Edwards (5), in an attempt to discover the mechanism of inheritance of susceptibility to tumor induction in certain strains of mice, repeated and extended Andervont's work. Injecting solid dye subcutaneously up to 1 year (100 mgm. total) they obtained liver tumors in 36 per cent

of C3H male mice surviving the full period. However, in strains A, C, and C57 black they used males and females, and obtained decided differences in the incidences for the two sexes. Thus in strain A, males yielded 45 per cent and females 100 per cent; in strain C, males 8 per cent, and females 100 per cent; C57 black mice resembled strain C, with males yielding 9 per cent and females 100 per cent. The following year Andervont and Edwards (3), comparing the activities of this dye and of DAB, used the same 4 strains, but administered a total of only 45 mgm. in olive oil solution. In this experiment strain C males yielded no tumors, compared with 75 per cent in females; C57 black mice were similar. The yield of liver tumors was low in C3H mice, but 1 female out of 8 was positive compared with none out of 9 males. Strain A males were not used, but 100 per cent incidence was found in the females of this strain. Andervont, White, and Edwards (6) extended the comparison of the two azo dyes to the feeding route, using only strain C mice. They induced hepatomas, lung tumors, and hemangioendotheliomas (especially of the lungs) with *o*AAT in most of the females and many of the males also. The sex difference observed when the dye was injected subcutaneously was found in the case of oral administration also, but it was not so definite.

Andervont and Edwards (4) also investigated the effects of graduated doses of *o*AAT injected subcutaneously as crystals into female mice of strain A. This revealed that 10 mgm. of dye was sufficient to induce hepatomas in 30 per cent of the mice receiving that dose by 1 year, whereas a 40 mgm. dose led to hepatoma in 10 per cent at 27 weeks and in 50 per cent by 52 weeks; 65 per cent had hepatoma by 1 year after a 60 mgm. dose. Thus the effect of the dye was to a definite degree proportional to the dose given, and the results of Law and of Morosenskaya, both of whom used 10 mgm. doses, were supported.

While Kirby (24) found a definite sex difference in the susceptibility of C57 black mice to the action of DAB on the liver, his results in this strain, and also in CBA and stock mice, with *o*AAT show no such difference. In the case of stock mice, 2 out of 3 surviving 233 days developed hepatoma (1 had proved secondaries), while 7 out of 7 females surviving 250 days had hepatoma (secondaries found in 3), the earliest in a female mouse being at 366 days. Cba mice showed no sex difference; 5 out of 6 males and 4 out of 5 females surviving 250 days died with liver tumors, although no metastases were found in this strain. But in C57 black mice, 6 out of 6 males and only 3 out of 5 females surviving 250 days had hepatoma, 1 male showing secondary deposits. Not more than 130 mgm. of *o*AAT was administered to any one

mouse, and, as Andervont and his group (5) used 100 to 110 mgm., it would seem that massive dosing is not responsible for the difference in results. The use of C57 black mice is common to, and makes comparable, the experiments of Law (26), of Kirby (25), and of Andervont and his associates (3, 5). Andervont, Grady, and Edwards (5) used solid dye, Andervont and Edwards (3) an olive oil solution, Kirby (25) used an arachis oil solution, whereas Law (26) used an olive oil solution plus solid dye. The results of Andervont and his co-workers would seem to indicate that the presence or absence of a solvent makes no difference to the unequal sex susceptibility, and it

whether the dyes be administered orally or by subcutaneous injection. Moreover, the total evidence available shows that *o*AAT is the most powerful carcinogen for mice of all the azo compounds yet tested. Tests with 2 other azo dyes are very desirable: first, the new carcinogen for rats, *m'*-methyl-*p*-dimethyl-aminoazobenzene (15, 29) and secondly, the hitherto unknown N,N-dimethyl-4'-amino-2,3'-azotoluene.

The advantage of the 2,3'-azotoluene molecule over the azobenzene molecule in mice is shown by the activity of 4'-hydroxy-2,3'-azotoluene which, in the hands of Law (26), yielded almost as many fibrosarcomas in C57 black mice as did *o*AAT; even the parent

TABLE II: EFFECT OF AZO COMPOUNDS AT THE SITE OF INJECTION IN MICE

Author	Azo compound	Route	Incidence of sarcoma						
			Mixed	A	C	C3H	dba	Cba	C57 black
Shear (43)	<i>o</i> AAT	SubQ		0/19					
Cook, Hewett, Kennaway, and Kennaway (10)	1, 1'-AN	"	1/16						
Law (26)	<i>o</i> AAT	"					0/30		13/30
	BY	"					1/30		6/29
	<i>o</i> HAT	"					0/24		11/30
	AT	"					0/22		5/20
Seligman and Shear (42)	AT	"		♀ 0/10					
Shear and Stewart (3, 17)	BY	"		♂ 0/10			♂ 0/10		
Turner and Mulliken (47)	<i>o</i> AAT	"			8/10 ⁹				
Andervont and Edwards (3)	<i>o</i> AAT	"		none	♀ 1/20 ¹⁹	♀ 1/8 ²⁰			♀ 3/21 ²¹
	BY	"		"	none				♀ 2/21 ²²
Kirby ¹⁰ (25)	<i>p</i> AAT	"	none						
	<i>p</i> AAB	"	"						
	<i>o</i> AAT	"	"					none	♂ 1/5 ²⁶
	BY	"	♂ 2/9 ²⁵	♀ none				"	" 1/5 ²⁷

is unlikely that a change of solvent would favor equality of susceptibility in the sexes. Law's low incidence (3 per cent) is presumably due to his low dosage. The explanation seems to lie in the time factor. The tumorous male mice in Kirby's C57 black series all died at an age later than that to which Andervont and his group allowed any of their mice to live. The sex difference in susceptibility observed by Andervont and his co-workers may therefore be one of latent period and not of susceptibility; this is certainly indicated by Kirby's results, but a different result might follow prolonged experimentation with smaller doses.

Summing up the position from the point of view of the azo compounds, one can say that the 3 groups of workers who have carried out comparative experiments with 2 or more azo compounds (3, 6, 25, 26) are agreed that 4'-amino-2,3'-azotoluene is much more carcinogenic for the livers of mice, either of mixed or pure strain, than is N,N-dimethyl-*p*-aminoazobenzene,

compound, 2,3'-azotoluene, yielded a higher percentage of these tumors than did DAB. On the other hand, the 4,5'-azotoluene molecule, at least when the amino group is in the 2'-position, seems to be inert; similarly, *p*-aminoazobenzene seems to be inactive in mice.

Whereas 2,3'-azotoluene seems to have no effect on the mouse liver, 2,2'-azonaphthalene causes tumors in a high proportion of animals, cholangioma being seen as early as 32 days after the initial dose was given (10). But 1,1'-azonaphthalene had only a slight action, and the 1,2'-isomer none at all.

B. TUMORS AT THE SITE OF INJECTION (SEE TABLE II)

The early workers, including Shear (43), reported no tumors at the site of injection, and it was not until Law published his results (26) that there was any reason to believe that azo dyes were sarcogens. Cook and his associates (10) had reported a very malignant

spindle and giant cell sarcoma 441 days after injections of 1,1'-azonaphthalene, but Law found a fibrosarcoma in a C57 black mouse injected subcutaneously with *o*AAT after only 45 days. Since Shear used *o*AAT in his experiments and, moreover, injected 7 times the amount used by Law per mouse, the effect of the solvent and/or strain was brought out very clearly; Shear used 70 mgm. crystals, Law an olive oil solution until 5 mgm. dye had been injected and then a 5 mgm. pellet. The first fibrosarcoma appeared before the pellet was introduced. It is interesting that Morosenskaya, who injected 10 mgm. *o*AAT dissolved in sunflower seed oil, observed no sarcomas at all, even at 8 months. The effect of the solvent was also brought out by the work of Andervont and his co-workers. Andervont (1) used crystals in his first experiment, and reported no sarcomas. Similarly, no sarcomas were reported by Andervont, Grady, and Edwards (5), who also used the solid dye. In one series (3) Andervont and Edwards injected *o*AAT in olive oil and then 3 out of 21 female C57 black mice died with sarcoma at the site of injection at or before 52 weeks; the same lesion was found in 1 female of strain C and in 1 of strain C3H. Even then, Andervont and Edwards found no sarcomas in mice of strain A. Kirby (25), using an arachis oil solution, obtained a spindle cell sarcoma containing giant cells at 252 days in a female of C57 black strain, but none in stock mice or in the Cba strain. On the other hand, Turner and Mulliken (47), using a corn oil solution of *o*AAT, found sarcoma in 8 out of 10 strain C mice at about 1 year.

While Shear and Stewart are reported (3, 17) to have found no sarcomas in strain A mice injected with crystals of DAB, and Andervont and Edwards (3) found none in mice of strains A or C injected with an olive oil solution of this dye, the latter authors found sarcoma in 2 out of 21 females of C57 black strain. The sarcogenic action of DAB was confirmed by Kirby (25), who found a mixed cell fibrosarcoma in a female C57 black mouse dying at 321 days after a total injection 127.5 mgm. of dye. Whereas no male C57 black mice developed a tumor at the site of injection (although 10 survived 250 days and Law obtained his first fibrosarcoma at about 50 days), 2 male stock mice developed spindle cell sarcomas related to the injections; no female stock mice showed such a lesion. The 2 male stock mice had received 157.5 and 172.5 mgm. of dye respectively, and the tumors were found at 344 and 379 days. Female mice of the Cba strain did not survive 208 days, but 12 males survived periods ranging from 374 to 565 days without showing any neoplastic reaction at the site of injection. Hence Cba mice were resistant both to DAB and to *o*AAT.

Law, using DAB in olive oil, found fibrosarcomas in C57 black mice (20 per cent), while AT was at

least as effective a sarcogen, and *o*HAT was nearly as powerful as *o*AAT.

The consensus seems to favor *o*AAT as the most powerful sarcogen for mouse subcutaneous tissues. Law's work places *o*HAT second, with DAB only half as powerful as *o*AAT. Other findings would indicate that DAB is much more nearly equal in power to *o*AAT. The result of Turner and Mulliken is remarkable, exceeding even the high activity found by Law for *o*AAT. In view of the favorable nature of corn oil for the development of liver tumors due to DAB fed to rats (31), it is tempting to speculate whether it specially favors sarcogenesis at the site of injection.

C. LUNG TUMORS (SEE TABLE III)

One of the earliest workers with azo dyes, Nishiyama (37), observed lung tumors in 1 out of 7 mice fed *o*AAT, and stated that the nodules were hemangioendotheliomas. Kirby found this lesion in the lung of a female stock mouse injected with *o*AAT in arachis oil; this mouse also had secondary hepatoma deposits. Andervont, White, and Edwards (6), who fed *o*AAT to strain C mice, obtained pulmonary tumors in 20 out of 29 males and in 27 out of 31 females; of these 47 lesions, 20 were hemangioendotheliomas. Similarly, Andervont, Grady, and Edwards (5), who injected *o*AAT as crystals subcutaneously into mice of strains A, C, C3H, and C57 black, found pulmonary tumors, including hemangioendothelioma, in 13 out of 24 strain C mice and in 18 out of 22 mice of strain A. The same 4 strains were employed by Andervont and Edwards (3), who injected *o*AAT in olive oil solution; lung tumors were found in 6 out of 7 strain A mice and in 14 out of 33 strain C. These authors also injected DAB in olive oil into A, C, and C57 black mice; C57 black strain mice never developed lung tumors, and the incidence in the A and C strains was not greater than the normal spontaneous figures. Law reported no lung tumors with any of the compounds he used, but Morosenskaya (36) found these lesions in an unrecorded proportion of P-B. mice receiving *o*AAT orally, cutaneously, or subcutaneously. Kirby found 1 adenoma in a female stock mouse after injections of *o*AAT, and in 1 male stock mouse after injections of DAB; mice of the Cba strain were free of any lung tumors.

The conclusion may be drawn that azo dyes have little capacity to provoke pulmonary tumors in mice, except in strains that are liable to spontaneous tumors of the lung. Andervont, Grady, and Edwards (5) concluded that "the response of the lungs of mice to *o*-aminoazotoluene injections was similar to that produced by hydrocarbons. In addition, the pulmonary

tive tissue nor was there extensive proliferation of bile duct epithelium toward cholangioma formation." This presumably refers to the effects of *o*AAT, *o*HAT, DAB, and AT; but adenomatosis of bile ducts was apparently found in 2 dba mice receiving *o*AAT. Andervont and his group, using *o*AAT (1, 3-6), found very little bile duct proliferation in mice of the A, C, C3H, or C57 black strains. Cholangioma was not reported by other workers except Kirby (25), who found following injection of *o*AAT considerable bile-duct proliferation with the formation of subcapsular cysts in Cba mice, and proliferation amounting to cholangioma in several stock mice of mixed origin. The latter result suggests that mice are not unable to react in this way to *o*AAT, and that a pure line might be found that was very susceptible to bile duct proliferation under the stimulus of *o*AAT. But the generalization remains that mouse liver shows a sharp divergence in reaction to azonaphthalenes on the one hand, and to *o*AAT and DAB at least, on the other.

The work of Opie (38) makes it clear that DAB can cause liver tumors in rats without cirrhosis at any stage, although the proportion of animals developing tumors increases with the severity of cirrhosis when it is present. Cirrhosis would appear to indicate a dietary deficiency either from the diet as ingested, or arising as the result of the removal, by one means or another, of some constituent of the diet in the alimentary canal or inside the body itself, especially in the liver. Deficient diets have been devised that induce cirrhosis; the presence of DAB in the diet may aggravate the cirrhosis, suggesting a metabolic antagonism of some kind in the liver itself. The picture for mice is not notably different from that for the rat. A focal increase in reticulum was usually seen following administration of *o*AAT, even when a full diet was given (1, 3, 5, 6, 25), and this was true for DAB (25). Andervont and his co-workers refer to the "cirrhotic appearance" of their mouse livers but say "there was no extensive fibrosis" (5); with this Law and Kirby agree. All strains of mice, as well as heterozygous mice, seem to show the same kind of lesion.

STRAIN SUSCEPTIBILITY

Apart from mice of mixed origin, 10 strains of mice have been used in experiments with azo compounds.

1. *M (leaden)*.—A few of these were injected by Shear (43), but it is not clear from his paper whether any of the lesions reported were in mice of this strain.

2. *P.-B.*—These were used by Morosenskaya (36), and showed themselves to be susceptible to liver tumor and lung tumor induction by means of *o*AAT by any of the 3 routes employed. Unfortunately, the proportion of animals actually developing tumors is not stated (17).

3. *dba*.—Mice of this strain were employed by Law (26), and by Shear and Stewart (3, 17). The latter found no tumors in males when DAB was given in solid form; Law found sarcoma in 1 out of 30 injected with DAB in olive oil, but no tumors at the site of injection with *o*AAT, *o*HAT, or AT. Law reported a very low incidence of hepatic tumors with DAB, *o*HAT, and AT also, and only 7 out of 30 with *o*AAT. This strain may therefore be regarded as rather resistant.

4. *Cba*.—This strain has been used only by Kirby (25). Liver tumors were found in most males and females injected with *o*AAT in oil; DAB in oil gave liver tumors in 3 out of 14 males, females not having been adequately tested. No sarcomas, lung tumors, or endotheliomas were found, and this strain appears to be susceptible only to liver tumor induction, although this includes definite bile duct proliferation.

5. *I*.—Strain I mice were used by Andervont (1), who injected solid *o*AAT. Two-thirds of the males and all the females developed liver tumors, but no other neoplasms were recorded.

6. *Y*.—Andervont also injected mice of this strain with solid *o*AAT. The results indicate a greater resistance than that possessed by the other 4 strains employed, namely, A, C, C3H, and I.

7. *C3H*.—Three series of experiments by Andervont and his co-workers concern strain C3H mice. Andervont's original experiment (1) yielded 100 per cent of liver tumors in males, but Andervont, Grady, and Edwards (5), who injected the same amount of dye, also as the solid, found only 5 out of 14 males surviving a year to have liver tumors. When the total dose was decreased to 45 mgm. and injected in olive oil, Andervont and Edwards (3) found no liver tumors in males and only 1 in 8 females; DAB in oil produced no liver tumors. The reasons for these differences are not apparent. Injections of *o*AAT caused 1 sarcoma and 1 endothelioma among all the mice used (about 50). Lung tumors were never found in this strain.

8. *A*.—Seven investigations have been made with mice of this strain; 3 by Shear and his collaborators (3, 17, 42, 43) and 4 by Andervont and his group (1, 3-5). AT and DAB caused no tumors at any site. On the other hand, 2 out of 22 mice in Andervont, Grady, and Edwards' experiments with solid *o*AAT developed hemangioendotheliomas; *o*AAT also caused lung tumors in a very large percentage of mice, far in excess of the spontaneous incidence in these animals. Liver tumors following *o*AAT administration were very common. The experiment of Andervont and Edwards (4), who injected graded doses of crystals into female mice, indicated a rise in incidence from 6 out of 20 after 10 mgm. to 13 out of 20 after 60 mgm.

Other experiments showed 100 per cent incidence among females receiving 100 mgm. *o*AAT. Males were usually more resistant, and it seems that females develop liver lesions more readily although the ultimate incidence may be the same. Subcutaneous injection of *o*AAT or DAB, even in oil, failed to evoke sarcoma in this strain.

9. *C.*—Baumann, Jacobi, and Rusch (7) fed *o*AAT and Turner and Mulliken (46) injected *o*AAT in corn oil, using strain C mice. Baumann and his associates reported premalignant changes in 100 per cent of their mice, and Turner and Mulliken found that 60 per cent developed liver tumors. Andervont's work shows a high degree of susceptibility to liver tumor induction by *o*AAT; this applies much more to females, 1 even developing hepatomas when fed DAB, than to males. Here again the sex difference may be one of latent period only. Turner and Mulliken found sarcoma in 80 per cent of their mice injected with *o*AAT, but Andervont and Edwards (3) saw this lesion in only 1 out of 20 females, using about one-third of the dosage given by the former workers. The work of Andervont and his group makes it clear that strain C mice respond very readily to *o*AAT with lung tumors and endotheliomas, the females again being more susceptible than the males up to 1 year. DAB elicited no tumors outside the liver.

10. *C57 Black*.—Law (26) encountered liver tumors in mice of this strain following injections of *o*AAT, *o*HAT, or even AT, though in the latter case the time was so long that spontaneous tumors cannot be excluded. Andervont and his collaborators (3, 5) found a much higher percentage of animals developing hepatomas, especially females. Kirby, also, obtained hepatomas in a high percentage of C57 black mice; DAB revealed a much greater susceptibility among females, but *o*AAT attacked male livers just as readily as female, though rather later. It is worth noting that Kirby saw no cholangiomatous lesions in this strain (25).

Law found sarcomas at the site of injection in this strain following *o*AAT, DAB, *o*HAT, and AT; in nearly 50 per cent in the case of *o*AAT. Andervont and Edwards (3) saw these lesions after injection of *o*AAT or of DAB, and Kirby obtained the same result but only in females. All three groups of workers agree that endotheliomas are caused by *o*AAT but not by DAB. No lung tumors were found by any investigator.

This review of strain susceptibility shows that the carcinogenic (or sarcogenic) power of an azo compound is not absolute, but depends on the strain of mouse employed in the test. Thus the sarcogenic power of *o*AAT, for example, would never have been discovered had investigations been confined to mice of strains A, Cba, and dba. On the other hand, all

strains investigated have shown some degree of liver tumor formation, but low doses may fail to evoke such lesions when higher ones would succeed. The only strain that developed liver, lung, connective tissue, and endothelial tumors was the C strain, but a full test for any azo compound would probably best be carried out by (a) feeding, and (b) subcutaneous injection in mice of strains A, C, and C57 black.

THEORIES OF THE MECHANISM OF TUMOR INDUCTION BY AZO COMPOUNDS

A. THE "SPLIT-PRODUCT" THEORY OF LIVER CARCINOGENESIS BY AZO DYES

The work of Kinosita (22) established that DAB is more carcinogenic for the liver of rats than the isomeric *o*AAT. Since the latter dye was shown by Hashimoto (18) to be metabolized in N,N'-diacetyl-*p*-toluenediamine when fed to rabbits, Kinosita suggested that DAB also would be split at the azo link by rats, and excreted as aniline and N,N'-dimethyl-*p*-phenylenediamine. The work of Stevenson, Dobriner, and Rhoads (44) confirmed the suggestion that reductive fission occurs, but the products excreted were *p*-aminophenol or its N-acetyl derivative, and *p*-phenylenediamine or its N,N'-diacetyl derivative. Hence demethylation occurred at some stage, but there was no evidence whether this took place before or after the azo link had been reduced and broken. Meanwhile Kensler, Sugiura, and Rhoads (20) had reported that the diphosphopyridine nucleotide content of rat livers was reduced during carcinogenesis by DAB and absent from the neoplastic tissue. Kensler, Dexter, and Rhoads (19) proceeded to show that a DPN system was inhibited by the partial oxidation products of various *p*-diamines, which could be regarded as derivable from azo dyes by reductive fission; they wrote that the degree of inhibition was proportional to the carcinogenic activity of the parent azo dye. Similar results for yeast carboxylase were obtained by Kensler, Young, and Rhoads (21), and for urease and succinoxidase by Potter (40). Since *p*-phenylenediamine itself had considerable inhibitory action against all 4 enzyme systems, the present author argued that *p*-aminoazobenzene ought to be carcinogenic if the 2 sets of facts are related; primary liver cell carcinoma with metastasis was actually obtained by prolonged feeding of this azo dye (20). Nevertheless, the table presented by Kensler, Dexter, and Rhoads on page 9 of their communication (19) contains one definite inaccuracy that weakens their argument. As Miller and Baumann (29) have pointed out, N,N'-dimethyl-*p*-aminoazobenzene is much more carcinogenic than the 4-methyl derivative although Kensler and his associates give both compounds the same value (+ +) for

this property, and both would yield the same fission product. Moreover, although the solubility of methyl orange in water might account for its noncarcinogenicity, this can hardly explain the absence of activity in 2(N,N-dimethyl-*p*-aminophenylazo)-naphthalene; both of these should yield N,N-dimethyl-*p*-phenylenediamine. Miller and Baumann have also found that N-methyl-*p*-aminoazobenzene is as strong a carcinogen for the liver of rats as is the fully methylated dye, and this is confirmed by Kensler and his associates (46), although from the relative inhibitory powers of the fission products, N-methyl-*p*-phenylenediamine and N,N-dimethyl-*p*-phenylenediamine respectively, one would have predicted only half the carcinogenic activity for the monomethyl compound. It must be borne in mind, however, that Miller, Miller, and Baumann (32) have shown the body capable both of methylating the monomethyl to the dimethyl compound and, conversely, of demethylating the dimethyl to the monomethyl compound, and the closely similar activities might be accounted for in this way.

Much more serious criticism arises from the findings of Miller and Baumann (29) with the *o'*, *m'*, and *p'* methyl derivatives of DAB. These would all yield N,N-dimethyl-*p*-phenylenediamine, yet the *o'*-compound has a carcinogenic activity for rat liver about one-third that of the parent dye and the *p'*-compound seems to be nearly as weak a carcinogen as is *p*-aminoazobenzene, whereas the *m'*-compound is even more active than DAB itself. It thus appears that the carcinogenic activity of azo dyes cannot be strictly correlated with the enzyme inhibitory powers of the diamines produced by reductive fission. Miller, Miller, and Baumann (32) further considered that demethylation may precede reductive fission, so that the highly inhibitory dimethyl-*p*-phenylenediamine would never be formed *in vivo*. If this is so, then *p*-aminoazobenzene and the dimethylated dye would both yield the same fission product, *p*-phenylenediamine, and the carcinogenic activities would bear no relation at all to the enzyme inhibitory power of the diamine.

B. THE "BENZIDINE REARRANGEMENT" THEORY

The great carcinogenic and sarcogenic power of 3,4,5,6-dibenzcarbazole for the skin of mice and for the subcutaneous tissues of mice and rats was demonstrated in 1937 by Boyland and Brues (8). The occurrence of bladder epithelioma among aniline dye workers, especially among those handling naphthylamines, led Cook, Hewett, Kennaway, and Kennaway (10) to investigate the effect of the azonaphthalenes administered to mice by the usual 3 routes—oral, cutaneous, and subcutaneous. Though no bladder tumors were obtained, 2,2'-azonaphthalene was shown

to cause liver tumors, 1,1'-azonaphthalene being slightly active and the 1,2'-isomer inactive. Cook and his collaborators argued that as azo compounds could undergo reductive fission in the body, hydrazo compounds are presumably formed and that the latter might also follow the alternative path of rearrangement to a benzidine type of compound. They therefore also tested the dinaphthyls carrying two amino groups *ortho* to the "benzidine type" bond that could arise by such a rearrangement of the 3 azo naphthalenes. Activity was confined to 2,2'-diamino-1,1'-dinaphthyl, which would be derived from 2,2'-azonaphthalene. As de-amination of this compound occurs very readily *in vitro* to yield 3,4,5,6-dibenzcarbazole, which is known to be a powerful carcinogen, Cook and his group suggested that 2,2'-azonaphthalene acts on the liver of mice because it is there converted to 3,4,5,6-dibenzcarbazole; the same process would explain the activity of the intermediate dinaphthyl.

In 1944 Elson and Warren (13) reported that they had isolated aniline from the urine of rats injected intraperitoneally with an arachis oil solution of azobenzene. This indicated that part of the azobenzene underwent reductive fission at the azo link. However, ether extraction of the acidified urine yielded benzidine, which they regarded as formed during the acidification stage from a soluble derivative of hydrazobenzene. The evidence showed that very small quantities of benzidine were present in the livers of rats receiving azobenzene. But preliminary results with rats receiving DAB showed that the actual "benzidine rearrangement" takes place more readily than in the case of azobenzene, and that a compound giving a color reaction, which they used as a test for "benzidine type" compounds, was present in the alkaline or neutral urine. The indications, then, are that in the rat azo compounds may, and DAB in particular does, follow 2 metabolic paths; one leads to the cleavage of the molecule at the azo link to provide amines such as aniline, while the other leads to benzidine type derivatives. Since Elson and Hoch-Ligeti (12) have found that "benzidine rearrangement" products of the latter type, when suitably oxidized, are strong inhibitors of urease and succinoxidase systems, it is clear that both metabolic routes can provide the means of enzyme inhibition, and hence of favoring carcinogenesis if Potter's views are accepted.

As the comparative carcinogenic activities of DAB and *o*AAT are reversed in mice as compared with rats, a theory that explains the greater activity of DAB in rats can hardly explain the greater activity of *o*AAT in mice. It may be suggested that reductive fission predominates in rats and leads to diamines known to have a certain order of inhibitory powers against rat

and plant enzymes. On the other hand, in mice the other path of "benzidine rearrangement" might predominate, and lead mainly to compounds having a different order of inhibitory powers against enzyme systems. Three questions need to be answered before a decision can be made. First, have the diamines tested by Kensler and his associates (19, 21) and Potter (40) the same order of toxicity toward mouse enzymes as they have toward the 2 rat and the 2 plant enzymes tested so far? Secondly, what are the metabolic products excreted by mice receiving azo compounds; are these the same as those excreted by rats and, if so, are the relative amounts excreted the same in rats and mice? Thirdly, have the "benzidine rearrangement" products the same order of toxicity toward enzymes as the "split product" diamines derived from the same azo compounds?

Meanwhile it is possible to postulate that the existence of the "split product" and "benzidine rearrangement" paths of metabolism is responsible not for the difference between the activities of DAB and *o*AAT in rats and in mice, but for the difference in the nature of the liver response to various azo compounds. The hypothesis of Cook and his group (10), that 2,2'-azonaphthalene is active against mouse liver by virtue of "benzidine rearrangement" and subsequent de-amination, implies that the type of tumor seen is linked with this metabolic pathway. Actually, cholangioma was the almost exclusive liver neoplasm seen after the administration of 2,2'-azonaphthalene. In rats both hepatoma and cholangioma follow administration of DAB or of *o*AAT, although cholangioma is less frequent with the latter dye (14); this may indicate a fairly equal importance of the 2 metabolic pathways following DAB administration, and a lesser importance of the "benzidine rearrangement" pathway for *o*AAT metabolism in the rat. In mice receiving DAB only hepatoma has been reported; this may be construed as indicating that reductive fission predominates. When *o*AAT is given C57 black mice, only hepatoma formation is seen and hence, possibly, the same pathway predominates. But stock mice of mixed origin and Cba strain mice, injected with *o*AAT, were shown by Kirby to be liable to develop cholangioma; in these mice the second, "benzidine rearrangement," pathway might be assumed to be utilized to a relatively greater extent. Until data regarding the actual metabolism of azonaphthalenes in mice, and of *o*AAT in stock, Cba, and C57 black mice, are available, this hypothesis must remain a speculation.

SUMMARY

1. The investigations into the action of azo compounds in mice reported in the literature are reviewed from the points of view of the azo compounds used, the lesions evoked, and the strains of mice employed.

2. The relative carcinogenicities of N,N-dimethyl-*p*-aminoazobenzene and 4'-amino-2,3'-azotoluene are shown to be reversed in mice compared with rats. Theories explaining the order of carcinogenicities in one species will not suffice for the other species.

3. The predominance of cholangioma in the livers of mice receiving azonaphthalenes, and other data for rats and mice, may indicate that metabolism of azo compounds to "benzidine type" derivatives favors bile duct proliferation, while "reductive fission" favors hepatoma formation.

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The Deterrent Effect of Light upon the Incidence of Spontaneous Mammary Cancer in Mice

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Many observers have noted the fact that cancer mortality rates vary in different parts of the world, even when peoples of the same European stock, but living in different climates, are compared. In 1941 a comparison by Apperly of the general cancer mortalities of the various Canadian provinces and American states showed that, in contradistinction to skin cancer, the mortalities fell with (a) increasing solar radiation, and (b) the number of people exposed thereto (1). Whether solar radiation is causally connected with this lowered mortality or not is unknown, but certain experimental work on animals suggests a direct relationship. Thus (a) Pearce and Van Allen (30) and Pearce and Brown (29) found in a series of experiments extending over 4 years that continuous exposure to light (Mazda and mercury arc lamps) lowers the malignancy (*i.e.*, incidence, mortality, and number of metastases) of transplanted cancers in rabbits. (b) Morton, Luce-Clausen, and Mahoney (26) found that, of 2 groups of mice painted with benzpyrene for 17 weeks, the group exposed to artificial daylight for 12 hours daily had fewer tumors (papillomas and skin cancers) than the group kept in darkness. The appearance of tumors was also delayed. (c) Doniach and Mottram (14) obtained similar results, but (d) Taussig, Cooper, and Seelig (35), using a General Electric type SI sun lamp, could find little difference between their groups.

Since no one, however, had reported similar work on spontaneous tumors, it was decided to investigate the effects of light on strains of mice subject to mammary cancer.

Our first experiments, begun in 1939 with 65 strain A mice, were published in 1942 (2). After preliminary tests to determine the best methods and times of exposure, the animals were irradiated with light from a G. E. model F ultraviolet lamp for 2½ minutes daily at 30 inches, in divided dosage or for 5 minutes 3 times a week. Exposure to larger doses than these had resulted in the development of ear and eye tumors. However, with the doses selected, none of these tumors developed, but an early reddening and later a slight

tanning easily distinguished the light-treated mice from the controls. As Table I illustrates, the incidence of spontaneous tumors was reduced from 80 per cent in the controls to 41 per cent in the irradiated animals. Although these experiments were suggestive, the number of animals used was too small to warrant definite conclusions. Accordingly a larger series was undertaken, which is the subject of the present report.

TABLE I

Number of strain A mice started.....	65	
Number of mice surviving to tumor age....	51	
Minimum tumor age.....	9 months 4 days.	
Foods: Purina dog chow checkers with a small amount of carrot		
	Controls	U-V light
Number of mice reaching tumor age.....	18	33
Of these:		
(a) Mice with one or more litters....	15	17
With breast tumors.....	12	7
Percentage with tumors.....	80 *	41
(b) Mice with no litters.....	3	16
With breast tumors.....	1	1
Percentage with tumors.....	33	6

* The normal incidence of breast cancer in this strain at Bar Harbor is 80 to 86 per cent.

RESULTS

In July, 1942, we began a new series of observations with 300 mice, then 6 weeks old, of the dba strain, subline I (strain A mice being then unavailable), which at Bar Harbor, Maine, have a spontaneous mammary tumor incidence of 80 per cent among breeding females, and 50 per cent among virgins. All animals were kept in metal cages in the diffuse daylight of a top-floor room lighted only by a ground-glass skylight window occupying about one-quarter of the ceiling area. Animals were not exposed singly to the ultraviolet lamp, nor were revolving or circular cages used. Instead, small groups were exposed in a square cage directly beneath the lamp, the animals being prevented from huddling by means of a stick or by changing the position of the cage at short intervals. All tumors were verified microscopically.

Of 161 mice that reached the tumor age of 10 months, there were (a) 60 control mice, not irradiated, of which 40 per cent had developed cancers when the experiment was terminated at the 131st week (Fig. 1); (b) 101 mice exposed to ultraviolet radiation,

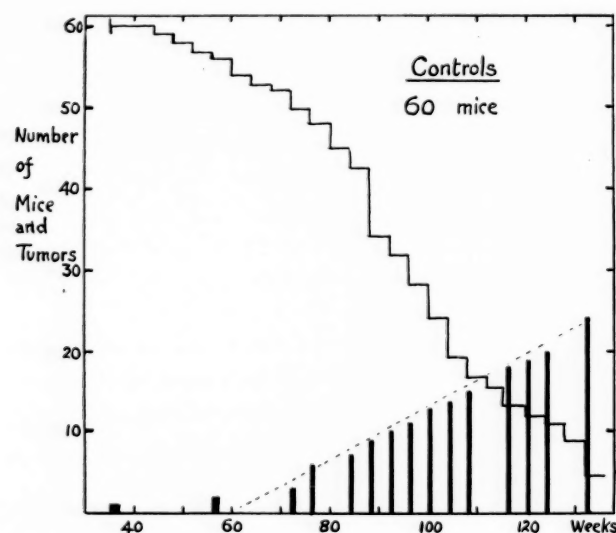


FIG. 1.—Control group, showing diminution in numbers of mice by deaths from all causes (upper curve), together with increasing total number of cancers (lower curve), at end of each 4 week period.

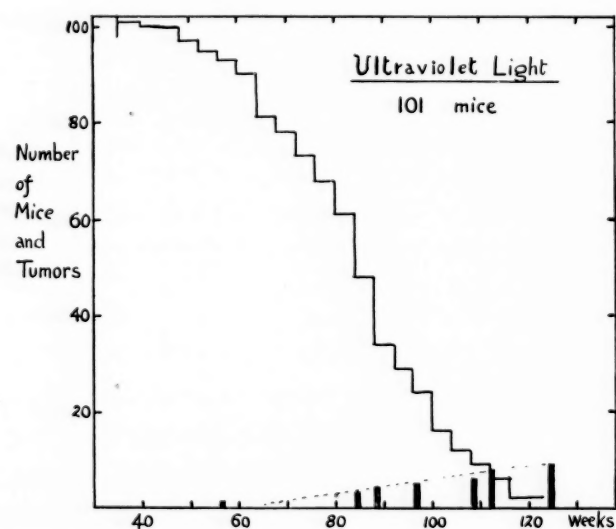


FIG. 2.—Ultraviolet-treated group, showing diminution in numbers of mice by deaths from all causes (upper curve), together with increasing total number of cancers (lower curve), at end of each 4 week period.

tion, of which only 9 per cent developed cancers (Fig. 2). The irradiated group, however, appeared to lose weight, to age earlier, and had a higher general mortality than the control group. Further, these mice bred earlier but less often, the litters being smaller and with a higher mortality. Unfortunately we did not weigh our animals from time to time.

A supplementary study was made to show the effects, if any, of the various forms of vitamin D administered from the age of 10 weeks. The 37 mice that reached tumor age belonged to 3 nearly equal subgroups. Three forms of the vitamin were used, *viz.*, viosterol (Abbott), ertron (Nutrition Research Laboratories), and vitamin D₃ (du Pont). Each of these was diluted to 2,000 units per cc., and administered orally by means of a fine pipette to all members of one or other of the 3 subgroups of mice, in doses of 0.02 cc. per gram of body weight per week. It is of interest that the rising curve of tumor incidence is apparently identical with that of the control series.

STATISTICAL ANALYSIS

The conditions described above permit statistical analysis in that the mice of all 3 groups were of the same strain, admitted to the study at an accurately stated age, and subsequently cared for in a manner identical in all respects but one, *viz.* the ultraviolet light treatment in the second group and the vitamin D treatment in the third.

In Table II are shown the size of samples used in all 3 groups, the number remaining alive as the study progressed, and the number of deaths with corresponding animal weeks at risk for each period of observation. The total period of observation extended over 100 consecutive weeks. In the light-treated group, however, the last mouse died at the end of the 88th week of study and at the end of the 76th week in the vitamin D treated group.

Based on the number of deaths due to cancer and animal weeks at risk for each period of observation, specific death rates were computed. Comparison of observed and expected deaths from cancer in the light-treated group is shown in Table III. The rates experienced in the control group were applied to the light-treated group in order to determine the association, or lack of association, of light treatment in mice and the incidence of cancer deaths. For purposes of statistical evaluation whereby consideration is given to the age factor of mice under observation Table III consists of 4 categories. These 4 groups supplying the basic data for determination of significant differences by means of the Chi-Square Test are presented in Table IV. The test shows a probability of similar findings approximately once in every 12 attempts, since *P* equals 0.05 to 0.10.

Table V has been constructed on the assumption that the mice in all groups were entirely comparable under the definitions of this study. It is possible on this basis to observe the number of survivors in each category at any given age. It would appear that for all 3 groups the mean age of 98 weeks is most critical,

since mice of greater age in the study die rapidly of senility if not from other specific causes.

Therefore, in the control group, if mice died from cancer only, 92 per cent would still be alive as compared with 97 per cent in the ultraviolet-treated group. The vitamin-D-treated mice would have less chance to survive, since only 82 per cent would remain alive. Of added interest is the fact that upon exclusion of cancer as a cause of death in mice, 86 per cent would live to be 98 weeks of age as compared with only

therefore the longevity of the light-treated mice was affected by the treatment, since such a difference could not have arisen by chance. The difference of 8.8 weeks between the control group and the vitamin D group is likewise significant, in that the reduction of the average life for vitamin-D-treated mice is 2.3 times the standard error. However, the difference between the light-treated group and the vitamin D group is but 3.7 weeks, and that difference is not significant based on standard error calculation.

TABLE II: EXPERIENCE TABLE FOR MICE IN STUDY

Weeks of observation	Mean age, weeks	Number alive at start of each period			Deaths						Animal-weeks at risk		
		Controls	Light	Vit. D.	Cancer			Other causes			Cont.	Light	Vit. D.
					Cont.	Light	Vit. D.	Cont.	Light	Vit. D.			
Total	36	60	101	37	24	9	11	36	92	26	3,544	4,718	1,862
1-4	38	60	101	37	1	0	0	0	0	0	238	404	148
5-8	42	59	101	37	0	0	0	0	1	0	236	402	148
9-12	46	59	100	37	0	0	0	1	4	0	234	392	148
13-16	50	58	96	37	0	0	0	1	1	0	230	382	148
17-20	54	57	95	37	1	1	0	0	0	0	226	378	148
21-24	58	56	94	37	0	0	1	2	4	2	220	368	142
25-28	62	54	90	34	0	0	2	1	8	0	214	344	132
29-32	66	53	82	32	0	0	0	1	4	2	210	320	124
33-36	70	52	78	30	1	0	0	1	6	1	204	300	118
37-40	74	50	72	29	2	0	0	0	4	1	196	280	114
41-44	78	48	68	28	1	0	0	0	7	1	190	258	110
45-48	82	47	61	27	1	2	1	3	10	1	180	220	104
49-52	86	43	49	25	2	1	1	4	11	2	160	172	94
53-56	90	37	37	22	1	0	3	5	5	3	136	136	76
57-60	94	31	32	16	1	1	0	1	7	8	120	112	48
61-64	98	29	24	8	2	0	0	3	8	1	106	80	30
65-68	102	24	16	7	1	0	2	4	4	2	86	56	20
69-72	106	19	12	3	1	1	1	1	3	0	72	40	10
73-76	110	17	8	2	0	2	0	1	0	2	66	28	—
77-80	114	16	6	0	3	0	0	0	0	0	58	24	—
81-84	118	13	6		1	0		0	4		50	16	
85-88	122	12	2		1	1		0	1		46	4	
89-92	126	11	0		0	0		2	0		40	—	
93-96	130	9			4			1			26		
97-100	134	4			0			4			—		

64 per cent in the light-treated group. Also, that if all causes of death are applied to both groups the treated mice have less chance to reach old age than do the controls, since 38 per cent die if left untreated.

With further reference to Table IV, if the mean age of 98 weeks was accepted as critical the effect of light treatment in reducing cancer incidence would be termed "significant," since *P* in this instance would approximate 0.05.

Table VI shows pertinent facts with respect to longevity in the 3 study groups. The controls live on the average 95.2 weeks, as compared with 82.7 weeks for those mice treated with ultraviolet light. The difference of 12.5 weeks is equal to 3.5 times the standard error and is, therefore, statistically significant. The standard error was calculated to be 3.6,

Table VII has been designed to show the number of mouse-months in the study for the several groups, and the general attack rate. For the entire study it will be noted that the light-treated group contributed more months at risk than did the controls. The number of actual deaths attributed to cancer, however, was significantly lower in the light-treated mice. The difference between 40 per cent cancer deaths in the control group and 8.9 per cent in the light-treated group is statistically significant, in that this difference is equal to 4.5 standard errors. However, since cancer deaths are so definitely correlated with age the significant difference just referred to cannot be considered wholly reliable. Therefore, the results obtained and shown in Table IV must be accepted as the least biased in this instance.

TABLE III: COMPARISON OF OBSERVED AND EXPECTED DEATHS FROM CANCER IN LIGHT-TREATED AND CONTROL MICE

Mean age	Controls			Light treated		
	Animal-weeks at risk	Cancer deaths	Specific death rate (per 1,000)	Animal-weeks at risk	Cancer deaths Expected Observed	
38	238	1	4.2	404	1.7	—
42	236	—	—	402	—	—
46	234	—	—	392	—	—
50	230	—	—	382	—	—
54	226	1	4.4	378	1.7	1
58	220	—	—	368	—	—
62	214	—	—	344	—	—
66	210	—	—	320	—	—
70	204	1	4.9	300	1.5	—
					—	—
					4.9	1
74	196	2	10.2	280	2.9	—
78	190	1	5.3	258	1.4	—
82	180	1	5.6	220	1.2	2
					—	—
					5.5	2
86	160	2	12.5	172	2.2	1
90	136	1	7.4	138	1.0	—
94	120	1	8.3	112	0.9	1
98	106	2	18.9	80	1.5	—
					—	—
					5.6	2
102	86	1	11.6	56	0.6	—
106	72	1	13.9	40	0.6	1
110	66	—	—	28	—	2
114	58	3	51.7	24	1.2	—
118	50	1	20.0	16	0.3	—
122	46	1	21.7	4	0.1	1
126	40	—	—	—	—	—
130	26	4	153.8	—	—	—
					—	—
					2.8	4

TABLE IV: EXPECTED AND OBSERVED DEATHS FROM CANCER IN LIGHT-TREATED MICE

Mean age of mice, weeks	Number expected to die (T)	Observed deaths (O)	$\frac{(T-O)^2}{T}$
38-70	4.9	1	3.10
74-82	5.5	2	2.23
86-98	5.6	2	2.31
102-130	2.8	4	.51
Total	18.8	9	8.15

DISCUSSION

These experiments on dba mice confirm our first experiments on strain A mice (2), *viz.*, that general irradiation by ultraviolet light under certain conditions of time and dosage brings about a diminution in the incidence of spontaneous mammary cancer. The mechanism by which light so acts is unknown, but there are several possible factors that deserve consideration. In any discussion of these factors one must always bear in mind that the application of results of other investigators, working with tumors of different

organs in different animals, to explain the mechanisms operating in spontaneous mammary cancer of dba mice is open to question. For this reason, therefore, we have generally restricted our references to those that seem to be of general application.

1. *Calcium metabolism.*—The most obvious connecting link between ultraviolet radiation and the diminished cancer rate in mice would seem to be the calcium metabolism. Calcium ions are necessary for the proper functioning of certain enzymes concerned in intracellular metabolism, such as adenosine triphosphatase, succinic dehydrogenase, acid phosphatases of liver, etc. In human and animal cancer, spontaneous and induced, one of the common (if not constant) findings is a hypocalcemia, both in the tumor tissues (5, 11, 16, 18) and in the serum of the host (22, 31, 33, 36). Further, some of the conditions that raise serum calcium, such as parathormone (28), acidosis (19), and calcium injections (23, 28), have been shown to prevent or lower the incidence of cancer in experimental animals, although they have no effect on existing tumors (32). It therefore seemed not

TABLE V: RESULT OF STUDY APPLIED TO 1,000 MICE IN EACH CATEGORY

Mean age, weeks	Period of observation	Controls			Light			Vitamin D		
		Cancer	Other	All	Cancer	Other	All	Cancer	Other	All
Total	x	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000	1,000
38	1	996	1,000	996	1,000	1,000	1,000	1,000	1,000	1,000
42	2	996	1,000	996	1,000	998	998	1,000	1,000	1,000
46	3	996	996	992	1,000	988	988	1,000	1,000	1,000
50	4	996	992	988	1,000	985	985	1,000	1,000	1,000
54	5	992	992	984	997	985	982	1,000	1,000	1,000
58	6	992	983	975	997	974	971	993	986	979
62	7	992	978	970	997	952	949	978	986	964
66	8	992	973	965	997	940	937	978	970	949
70	9	987	968	955	997	921	918	978	962	941
74	10	978	968	945	997	908	905	978	953	933
78	11	973	968	940	997	883	881	978	944	925
82	12	967	952	918	988	843	833	968	935	907
86	13	954	928	883	982	789	775	957	915	878
90	14	947	894	844	982	761	747	824	879	722
94	15	939	887	830	973	713	693	824	732	601
98	16	921	862	791	973	642	624	824	708	581
102	17	910	821	744	973	596	580	742	637	465
106	18	897	810	723	949	551	522	668	637	418
110	19	897	798	712	882	551	485			
114	20	850	798	675	882	551	485			
118	21	833	798	661	882	413	364			
122	22	815	798	646	661	310	273			
126	23	815	758	614						
130	24	689	729	496						

TABLE VI: LONGEVITY IN STUDY GROUP

Study groups	Number mice in study	Average age lived, weeks	Average time of study, weeks	Standard deviation of mean age
Control	60	95.2	59.1	24.1
Light	101	82.7	46.7	18.3
Vitamin D	37	86.4	50.3	14.8

TABLE VII: MOUSE-MONTHS AT RISK IN STUDY AND ATTACK RATE FOR CANCER IN STUDY GROUPS

Study groups	Mouse-months in study	Monthly attack rate per 100	Cancer deaths	Mice dying from cancer, per cent
Controls	817.85	2.93	24	40.0
Light	1,088.77	.83	9	8.9
Vitamin D	429.69	2.56	11	29.7

unlikely that ultraviolet radiation might act by bringing about an increase of vitamin D and hence of serum calcium, and therefore lower the incidence of spontaneous breast cancer in mice. As Fig. 3 shows, however, this is apparently not the mechanism by which these results are produced, and the failure of vitamin D to influence tumor growth has also been noted by others (17). Thus it is probable that the low serum calcium is a secondary effect.

2. *Heating effect.*—Another possibility is that the anti-cancer effect of ultraviolet light is a heating effect. Several observers have shown that experimental cancer rates are diminished in heated rooms, and by artificial fever of various kinds (37, 39, 40), and it

seemed possible that light irradiation might act by heating the bodies of the animals treated. It was, for instance, interesting that our dba mice, which at Bar Harbor had an 80 per cent spontaneous mammary cancer rate, had only 40 per cent in the breeding female controls at Richmond, Virginia. On the other hand, the 86 per cent incidence of mammary cancer in strain A mice at Bar Harbor was practically unaltered in Richmond.

Actual observation showed that the average rectal temperature in 10 mice following ultraviolet irradiation under the conditions of our experiments rose by only 0.7° C., and returned to normal in about 1 hour. The total period of raised temperature therefore was no longer than 3 hours per week. The amount and duration of this pyrexia was, however, so much less and the diminution of tumor incidence so much greater than those of the authors reported above, that we find it difficult to involve temperature changes as more than a small factor in the explanation of our results.

3. *Weight loss.*—Just before completion of the present experiments Blum(6) published results of some similar work, which confirmed our previous report. In his discussion he pointed out that irradiated mice have a lower food intake, and hence body weight, than the controls (7), conditions that in turn have been shown to decrease the incidence of tumors in certain cases (34). The weight loss in our own mice was also noted, but unfortunately not measured. Weight

reduction produced solely by caloric restriction, however, results in increased longevity (34), but in our mice the weight loss associated with ultraviolet irradiation apparently had the opposite effect. It would therefore appear that the mechanisms in the 2 instances are different, and that the tumor reduction is dependent on some mechanism other than weight reduction. Blum's explanation, again, obviously does not apply in the case of human cancer in its relation to solar radiation.

4. *Hormonal exhaustion.*—Sex hormones, adrenocortical hormones, vitamin D, adenylic acid (an essential part of adenosine triphosphate and other essential enzymes of intracellular metabolism), and other sub-

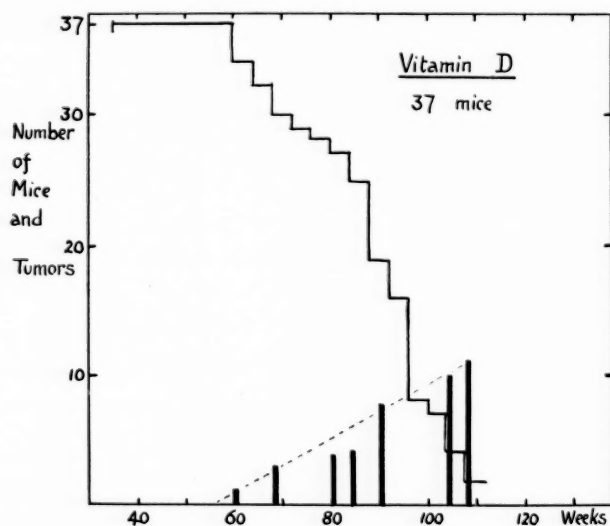


FIG. 3.—Vitamin-D-treated group showing diminution in numbers of mice by death from all causes (upper curve), together with increasing total number of cancers (lower curve), at end of each 4 week period.

stances are formed as the result of a series of chemical reactions, of which photochemical action in the skin is an early step (38). Our mice lost weight, became apparently decrepit and aged, and on the whole had a shorter span of life than the control group. Since senile atrophy is accompanied, and indeed even said to be caused, by gradual failure of the endocrine system (25), the suggestion presents itself that the ultraviolet light treatment of our mice resulted in an overproduction and finally an exhaustion of their endocrine systems, including the estrogens (an important factor in mammary cancer), with the final results already referred to. There is reason to believe that these activities may depend upon the reticuloendothelial system, discussed below.

5. *Reticuloendothelial activity.*—The reticuloendothelial system has been shown, by abundant clinical and experimental observations, to be in some way concerned in neoplasia. *Inter alia*, the evidence shows

that this system produces some substance that is inimical to malignant growths (8), and conversely, that reticuloendothelial atrophy (3, 13, 27) or blocking (4, 9) favors tumor growth. Among the stimulants of reticuloendothelial activity is total body ultraviolet irradiation (15, 24), which might therefore be expected to diminish the incidence of malignant tumors when the dosage is restricted to the proper amounts as we have shown. The mechanism by which these effects are brought about is unknown, but there is evidence that the cells produce some substance necessary for purine metabolism (10, 12) and therefore possibly involving the activities of such purine derivatives as adenosine triphosphate, coenzymes I and II, and flavin adenine nucleotide, enzymes essential for the oxidation of carbohydrates, whose failure is believed to be the immediate cause of neoplasia. It may be that this is the mechanism by which ultraviolet light influences the production of adenylic acid, already referred to.

The reticuloendothelial system is necessary for the production of antiestrogenic hormones (20, 21) also, and ultraviolet stimulation of this system might therefore be expected to curb the estrogenic factor in mouse mammary cancer, and possibly even lead to the exhaustion of hormones and the early senility noted by Blum and ourselves. The varying results of ultraviolet light in cancer might, from the considerations described above, be the resultant of 2 opposite effects, *viz.*, photochemical action in the skin resulting in the production of estrogens, vitamin D, and so on, and stimulation of reticuloendothelial cells leading to the production of antihormones, the final result depending on the balance between those 2 with varying dosage of ultraviolet radiation.

SUMMARY

In an attempt to explain the fact that the cancer mortality rates in the various states and provinces of the United States and Canada vary inversely as the solar radiation and the number of people exposed thereto, mammary cancer strain mice were exposed to light from a G. E. model F ultraviolet lamp for varying periods.

Of 161 mice that reached tumor age, 60 control mice showed a cancer incidence of 40 per cent when the experiment was terminated at the 131st week. Of 101 mice exposed to ultraviolet radiation only 9 per cent developed cancers, but the noncancer death rate was significantly increased.

The application of specific death rates throughout the study gives a *P* value of 0.05 to 0.10, which indicates "probable significance." A study covering 98 weeks of observation gives a "significant" *P* value of

0.05. Vitamin D is apparently not a factor in these experiments. Other possible factors are discussed.

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The Relationship of Caloric Intake and of Blood Sugar to Sarcogenesis in Mice*

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The retarding influence of caloric restriction on the genesis of tumors is now well known, but very little evidence is available concerning the mechanism of this action. In a previous report from this laboratory it was suggested that an abundant diet would furnish surplus energy for the growth of tumor cells even after the ordinary bodily requirements had been met, whereas on a restricted diet the supply of nutritive elements would be limited to a degree that would adversely influence the proliferation of neoplastic cells (11). Since tumors have been shown to possess a less efficient mechanism for obtaining energy from glucose (17), presumably an abundant supply would be necessary if such a tissue were to compete with normal cells for this substance. Therefore an estimation of the blood-sugar level in mice on high and low calorie diets and a correlation of these findings with the rate of cancer formation in such animals is of considerable importance.

It is also possible that various ratios of protein, carbohydrate, and fat in equicaloric diets influence the level of blood sugar and the rate of tumor development. Forbes and Swift (1) have demonstrated that the specific dynamic effect of a given nutrient depends upon the proportion of the other nutrients in the diet; thus the proportion of certain nutrients might determine the efficiency with which some foods are utilized. Previous work from this laboratory, for example, indicates that the formation of neoplasms can be accelerated by increasing the fat content of equicaloric diets (11). The present experiment was designed, therefore, to test the effect of equicaloric diets containing various proportions of proteins, carbohydrates, and fats on the rate of sarcogenesis, and to determine at regular intervals the blood-sugar level of mice on such diets.

MATERIALS AND METHODS

Eight groups of 40 strain C male and female mice from 3 to 4 months of age were placed on diets having as variables high and low calories, high and medium protein, and medium and low fat (Table I). Each

group contained 20 male and 20 female mice; the animals of each sex were kept on wood shavings in separate metal box cages. The diets were calculated so that all 8 groups received the same amount of salts and vitamins, while protein and fat varied in a regulated manner. Total calories were altered by feeding smaller amounts of diet, as well as by interchanging carbohydrate and Fisher "Ruffex". All calculations were based on the low-calorie:low-fat diet having casein at the level of either 20 or 40 per cent. The animals were allowed water *ad libitum*, and the amount of food was carefully weighed each day and placed in the cages at 9:30 A.M. A weekly record of the average weights of the groups was kept.

At intervals of 1 month the blood-sugar level of 5 mice from each group was determined from 3 daily samples taken at 9 A.M., 2 P.M., and 7 P.M., and the results are expressed as averages of the 15 samples obtained from each group. The mice used for these determinations had their ears marked so that the same ones were used each time and thus individual records could be kept. In order to obtain 3 samples of blood from each mouse in a single day without adversely disturbing the blood picture it was necessary to devise a technic for the removal of a very small amount of blood at each determination. This was accomplished with the aid of a red blood cell pipette selected to contain exactly 1.2 cc. When the pipette was filled to the 0.5 mark, as in doing a red blood cell count, the dilution as shown by colorimetric test was exactly 1 to 200. With this method only 0.006 cc. of blood was taken from each mouse for any one determination. In order to remove contaminating substances that might introduce a source of error, care was taken to wash the end of the tail thoroughly with water before cutting the tip with a sharp razor.

Miller and Van Slyke's modification (6) of Fujita and Iwatake's deproteinization technic was used to prepare the blood for analysis, except that double centrifugation and the removal of an aliquot of the supernatant was substituted for the filtration technic. The 0.006 cc. sample of blood was diluted to 1.2 cc. in the blood pipette with the acid cadmium solution, placed in a 2 cc. test tube, and 0.6 cc. of 0.275 N NaOH

*This investigation was aided by a grant from the Jonathan Bowman Fund for Cancer Research.

TABLE I: COMPOSITION OF DIETS

Type of diet	1		2		3		4		5		6		7		8	
	Low-calorie: Low-fat: Medium-protein		High-calorie: Low-fat: Medium-protein		Low-calorie: Medium-fat: Medium-protein		High-calorie: Medium-fat: Medium-protein		Low-calorie: Low-fat: High-protein		High-calorie: Low-fat: High-protein		Low-calorie: Medium-fat: High-protein		High-calorie: Medium-fat: High-protein	
Constituents	Gm. / mouse / day	Cal. gm.	Gm. / mouse / day	Cal. gm.	Gm. / mouse / day	Cal. gm.	Gm. / mouse / day	Cal. gm.	Gm. / mouse / day	Cal. gm.	Gm. / mouse / day	Cal. gm.	Gm. / mouse / day	Cal. gm.	Gm. / mouse / day	Cal. gm.
Cerelose *	60.2	1.08	204.4	3.4	33.8	0.54	115.0	1.8	34.2	0.61	116.4	1.8	47.0	0.72	198.0	3.0
Cascein	20.0	0.36	88.0	1.3	22.5	0.36	99.0	1.5	40.0	0.72	176.0	2.6	45.0	0.72	198.0	3.0
Corn Oil	2.0	0.04	18.6	1.3	14.6	0.23	136.0	9.8	2.0	0.04	18.6	1.3	14.6	0.23	136.0	9.8
Salts	4.0	0.07	0.0	2.7	4.5	0.07	0.0	3.0	4.0	0.07	0.0	2.7	4.5	0.07	0.0	3.0
Vitab †	2.0	0.04	5.2	1.3	2.3	0.04	6.0	1.5	2.0	0.04	5.2	1.3	2.3	0.04	6.0	1.5
Fisher Ruffex ‡	11.8	0.21	0.0	1.9	22.3	0.36	0.0	4.2	17.8	0.32	0.0	5.7	28.9	0.46	0.0	8.3
Total	100	1.8	316.2	100	100	1.6	356.0	100	100	1.8	316.2	100	100	1.6	356.0	100
Calories per mouse per day	5.7		9.3		5.7		9.3		5.7		9.3		5.7		9.3	

Each kgm. of diet contained also 80 mgm. of halibut liver oil.

* Cerelose. A pure glucose monohydrate containing 91% glucose. Obtained from the Corn Products Refining Company.

† "Vitab" rice bran concentrate. Carbohydrates compose 62% of "Vitab", a source of the B vitamins obtained from the National Oil Products Co., Harrison, N. J.

‡ A pure cellulose product prepared from rice hulls. Formerly known as Cellurition. Obtained from the Fisher Scientific Co., Pittsburgh, Pa.

Calories calculated on the following basis (See Bonassky, M. Introduction to Physiological Chemistry. Fourth Edition. New York: John Wiley and Sons, Inc., 1938, p. 510):

1 gm. casein = 4.4 cal.

1 gm. cerelose = 3.4 cal. (contains 91% glucose).

1 gm. corn oil = 9.3 cal.

1 gm. "Vitab" = 2.6 cal. (Vitab = 62% carbohydrates and 1.3% proteins).

added. After the contents were uniformly mixed they were heated in a boiling water bath for 3 minutes, cooled in running tap water for 2 minutes, and approximately 0.1 gm. of powdered BaCO_3 was added. The contents were shaken vigorously for 10 seconds, centrifuged, transferred to another tube, centrifuged again, and then a sample, usually 0.3 cc., was taken for analysis. Reinecke's (9) method for the determination of glucose in minimal quantities of blood was scaled down as follows: The 0.3 cc. aliquot was placed in a colorimeter tube, 0.6 cc. of $\text{K}_3\text{Fe}(\text{CN})_6$ added, and the tube heated in boiling water for 15 seconds; 0.6 cc. of cyanide-carbonate buffer was added, the tube covered with a glass bulb and again heated on the water bath, but this time for 15 minutes. The tube was then cooled in ice water to 30° , 0.6 cc. of ferric iron-gum ghatti reagent added, the contents were diluted to 3 cc. with water, and the tubes read in 45 minutes at $650 \text{ m}\mu$ with a Cenco-Sheard spectrophotometer.

In order to allow a sufficient time for the mice to become fully adjusted to the rations, the first blood sugar determinations were performed 50 days after the animals had been placed on the special diets. On the day following the first blood sugar analyses each mouse was injected subcutaneously in the back with 200 $\mu\text{gm.}$ of 3,4-benzpyrene in 0.2 cc. of corn oil. The mice were examined for tumors at weekly intervals, and when nodules appeared their length, width, and height in cm. were carefully measured with a calipers and their size was recorded as the product of these 3 dimensions.

RESULTS

Most of the animals appeared sleek and healthy throughout the experiment, and the survival was excellent. No more than 2 deaths occurred in any 1 group prior to the appearance of the first neoplasm. With the exception of Group 7, where there were 7 deaths, the number of mice dying of nonneoplastic disease before the termination of the experiment at 9 months in any 1 group was less than 4.

During the first part of the experiment the mice on the low calorie diets were allowed 6.2 calories/mouse/day, and all the mice in these groups lost weight rapidly during the first 10 days of the experiment, with an average loss that varied from 1.5 gm. for the group on the low-calorie:medium-fat:medium-protein diet (Group 3) to 2.5 gms. for those on the low-calorie:low-fat:medium-protein ration (Group 1). Nevertheless, under the conditions of this experiment, the mice on these low calorie diets gradually regained their original weight, and 1 month after the beginning 2 of the groups had exceeded it (Fig. 1). The weights then began to level off until

toward the end of the second month, when a sharp increase was again observed. This stabilized at about the 65th day, and thereafter the mice showed no tendency to lose weight. Because it was thought desirable to have a greater spread in body weights between the mice on low and high calorie rations, the intake of those on the low calorie diets was reduced to 5.7 calories/mouse/day on the 75th day of the experiment. This was followed by a prompt fall in weight that continued gradually for the remainder of the experiment, except for slight gain around the 100th and 160th day. A more rapid decrease in weight occurred toward the end of the experiment, coinciding with the appearance of tumors. The average weights of 3 of the groups on the low calorie diets remained very close throughout, whereas the

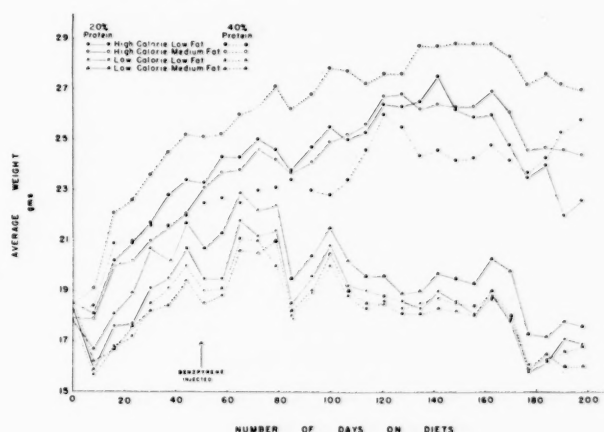


FIG. 1.—Weight record.

weight of Group 3 (low-calorie:medium-fat:medium-protein) was slightly but consistently higher.

Mice on the high calorie diets gained weight rapidly at first, then more slowly until the fourth month, when they reached an equilibrium; a gradual decrease was observed during the last month of the experiment. A considerable variation in weight was observed in these groups. Group 8 (high-calorie:medium-fat:high-protein) remained the highest and Group 6 (high-calorie:low-fat:high-protein) the lowest throughout most of the experimental period, whereas Groups 2 and 4 were intermediate.

Fluctuations were more evident in the mice on the restricted diets than in those receiving an abundant supply of food. The sharp gains observed in the former groups (Fig. 1) were correlated with periods of elevated room temperature. Since the mice consumed the same amount of food at times when the temperature was elevated as they did when it was lower, differences in metabolic requirements were reflected in changes in body weight, and it is not surprising that the mice on the high calorie diets

were less sensitive to differences in room temperature. A considerable portion of the experiment was conducted during the summer months, when the greatest variation in room temperature was observed.

The mice were fed only once each day, and the time required for the different groups to consume their food varied considerably. Those on the low caloric diets ate their allotment ravenously in from 3 to 6 hours, whereas the groups on the high caloric diets took from 6 to 24 hours. The mice on the high-calorie:medium-fat:high-protein (Group 8) finished their ration in from 6 to 10 hours, whereas those on the high-calorie:low-fat:high-protein (Group 6) required almost the entire 24 hour period. Actually certain groups in this series could easily have eaten more than the 9.3 calories/mouse/day, but for uniformity they were restricted to the amount that

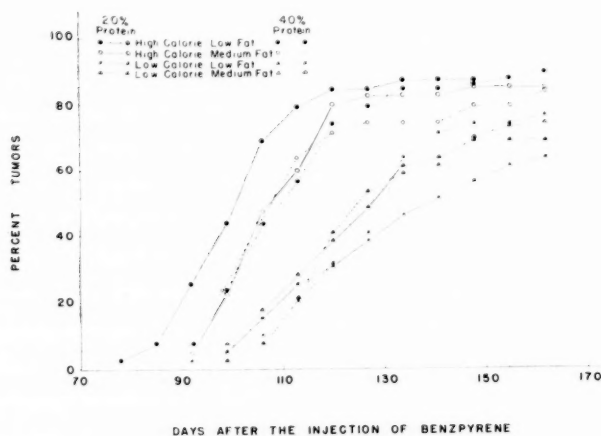


FIG. 2.—Time of occurrence of sarcomas in mice on several different diets following the subcutaneous injection of 3,4-benzpyrene.

would be consistently eaten by the most readily satisfied group.

Tumors appeared earlier in the 4 groups receiving the high levels of calories than in the restricted groups, and the rate of formation was also more rapid in the former (Fig. 2). Thus 120 days after the benzpyrene injection the incidence of sarcomas in the high calorie groups varied from 70 to 85 per cent, in contrast to the restricted groups, where the incidence was from 32 to 42 per cent. The rate of tumor formation was much more gradual in the mice on the restricted diets, and when the experiment was terminated, 160 days after the injection of the hydrocarbon, the percentage of tumors varied from 62 to 78 per cent, in contrast to the 84 to 90 per cent observed in the mice fed the high calorie diets.

The most rapid onset of tumor formation was observed in the high-calorie:low-fat:medium-protein group (Group 2), but the subsequent rate was the

same in this group as in the other abundantly fed groups (Fig. 2). The slowest rate was obtained in Group 1 (low-calorie:low-fat:medium-protein). Although a general correlation existed between the weight curves of the high and low calorie groups and the rate of tumor onset in these groups, there was no apparent correlation when single groups of either high or low calorie mice were compared.

A considerable variation was observed in the individual determinations of the blood sugars obtained from mice at different periods of the day. In general, the differences were less pronounced in mice on the abundant diets than in the animals kept on a restricted intake. The mice in most of the high calorie groups had food available for most of the 24 hours, and had no fasting period. The situation was different with those kept on the restricted diets, however, since they ate their daily allotment within a few hours after it was placed in the feeder at 9:30 A.M., and the blood samples taken at 9 A.M. and 7 P.M. may be regarded as typical of a fasting period, whereas the sample obtained at 2 P.M. represents a period of food ingestion. These eating habits were reflected in the level of blood sugar, especially during the early part of the experiment when the amount of reducing substances in the blood was usually highest in the samples obtained at 2 P.M. in the mice on the restricted diets. Such differences became less pronounced after several months. At all events, because of these variations the results are given as average daily values for a group to avoid presenting the 600 individual determinations.

With one exception the average daily blood sugars of the mice on the high-calorie diets were higher than those observed for the animals on restricted rations. The blood sugar of the mice on the high-calorie:medium-fat:high-protein (Group 8) averaged about 119 mgm. per cent for the 5 mice at the first reading, but this was reduced to approximately 100 one month later and then fell slightly below the average values for the mice on the low-calorie:low-fat:medium-protein group (Group 1, Fig. 3).

The first blood-sugar values for the mice on the high calorie diets were considerably higher than those obtained on subsequent readings. This was most pronounced in the case of Groups 2 and 4 receiving the medium protein, where the values dropped on an average of 40 mgm. per cent between the first and second readings, while the values in Groups 6 and 8 receiving the high level of protein dropped about 18 mgm. per cent between the first and second readings. Furthermore, the subsequent trend of the sugars of the former groups continued a gradual decline in contrast to the more stable character of the curves obtained for the latter groups. In general the

blood sugars tended to be higher in the mice receiving the medium protein than they were for the groups getting 40 per cent protein. The blood sugars of the low calorie groups were more constant throughout the experiment than was the case with the groups on the abundant diets. The values for the medium protein groups, 1 and 3, showed a gradual rise and the readings remained higher than for the low calorie groups getting high amounts of protein (Groups 5 and 7, Fig. 3). A fall in blood sugar was observed at the end of the experiment in all the groups, which was correlated with the appearance of sarcomas and a decrease in body weight.

When tumors were found their rate of growth was followed at weekly intervals by measuring their width,

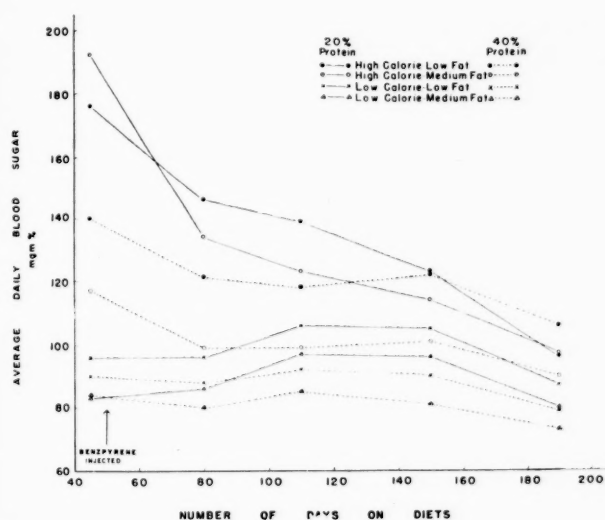


FIG. 3.—Level of blood sugar of mice at different times throughout the experiment. Each point represents the average of 15 separate determinations (the values from 3 daily readings obtained from 5 mice).

length, and depth. There was no conspicuous difference among the animals on the restricted and abundant diets, although a slight tendency to a somewhat more rapid growth rate was observed in the well fed groups. However, the results are further complicated by the wide variations in the rate of growth of the neoplasms among the individual mice of the different groups. One must conclude, therefore, that the effect of caloric restriction as employed in this experiment has only a negligible effect on the growth of established sarcomas.

DISCUSSION

The retarding effect of caloric restriction on the formation of sarcomas following the subcutaneous injection of 3,4-benzpyrene into mice is in accord with other similar experiments (10, 11). Although there was no striking difference in the initial appearance of

sarcomas in the mice on high and low caloric intake, the rate of formation was considerably less in the latter group. Thus 120 days after injection of the 3,4-benzpyrene 30 to 40 per cent of the mice on low calorie diets had palpable tumors, in contrast to an incidence of 70 to 80 per cent in those on high calorie diets. These results compare favorably with those reported by Tannenbaum (14) following the subcutaneous injection of benzpyrene, but the difference in tumor incidence between the mice on abundant and restricted diets is not as conspicuous as when mice developing spontaneous mammary carcinomas were used as the test animal (15) or when ultraviolet irradiation was employed as the carcinogenic agent (11). Perhaps a wider spread in time of tumor occurrence and rate of neoplastic formation might have been obtained in the present experiment if the dose of 3,4-benzpyrene had been reduced to 100 μ gm. per mouse, and if a greater spread in caloric intake between the groups on high and low calories had been instituted in the beginning.

The present experiment is complicated by the fact that the room temperature did not remain reasonably constant during the early period of the test. Although the room temperature had little effect on the body weight of the mice on abundant diets, it did have considerable influence on the weights of the restricted mice. A substantial elevation of room temperature was always accompanied by an increase in body weight in the latter groups. It is imperative, therefore, that experiments of this type should be done in rooms maintained at a constant temperature.

The mice on the abundant diets had high levels of blood sugar and developed tumors more rapidly than those on restricted diets, and the group with the highest average blood sugars (Group 2) also developed tumors most rapidly. The correlation is not complete, however, since tumors developed as rapidly in the mice of Group 8 (high-calorie:medium-fat:high-protein) as in other groups on high caloric diets, yet the level of blood sugar for this group was comparable to that observed in the mice on restricted diets. This relatively low blood sugar may have been due to the fact that the mice on this diet weighed more than those of any other group, and as a result received less diet per gm. of body weight than the other groups. Furthermore, a large proportion of their total caloric intake was in the form of fat and protein instead of glucose. Thus approximately 57 per cent of the total caloric intake in Group 8 is made up of protein and fat, as compared to 20 per cent for Group 2, 41 per cent for Group 4, and 37 per cent for Group 6. This may be of considerable importance, since Forbes and Swift (1) have pointed out that the specific dynamic effect of a given nutrient depends upon the propor-

tion of other nutrients in the diet. The blood sugar content would not be expected to be the limiting factor in tumor development under all circumstances; in Group 8 some other factor must have been more critical. Nevertheless, in the low-protein groups the blood sugar level actually appears to be correlated with tumor incidence, as well as with caloric intake, when this was varied by alteration in carbohydrate intake.

The results of this experiment tend to favor the previously stated theory that a well nourished animal has a better supply of available nutriment for the growth of a tumor after the ordinary requirements of the body have been met. This experiment indicates that glucose could be one of the factors available in excess in abundantly fed mice, but no doubt there are other unknown factors of equal or greater importance. One tentative explanation for the results of this experiment receives support if one assumes that blood sugar may have some influence on the critical period of neoplastic formation. The results can be readily explained if one assumes a critical period in neoplastic formation (4, 8). A favorable environment containing a high level of glucose in the tissue fluids probably would favor the proliferation of small nests of neoplastic cells that must compete with the normal tissues for the available building blocks. Several investigators have suggested a disturbance in the metabolism of glucose in patients with cancer. Thus Singher (12), for example, has recently observed that persons with cancer have a reduced glucose tolerance and an impaired ability to form and store glycogen in the liver. The pattern of the blood sugar in these patients, with the diminished rate of return to normal, would be comparable to the findings observed in the present experiment with the mice on a high caloric intake. Thus in both the human patients and the mice on abundant diets a high level of energy is available that would favor the growth of neoplasms.

No evidence that covers all the facts has yet been presented to explain the mechanism by which caloric restriction will inhibit tumor formation. A deficiency of certain amino acids has been shown to retard carcinogenesis (16), but in the present experiment the mice received a sufficient supply of these substances. The weight loss that results from caloric restriction might also be incriminated as an important factor in the inhibition of tumor development. It is true that if young mice are placed on restricted diets they fail to grow normally and appear to be in poor condition as compared to the control animals (2). However, when adult mice are employed caloric restriction results in an initial loss of weight, but the weight soon becomes stabilized and with a diet containing the

necessary ingredients the mice are thin but sleek and remain in excellent health throughout the period of experimentation (11, 14). McCay and his associates (5) report that rats on restricted diets outlive those allowed food *ad libitum*.

It has been proposed that caloric restriction interferes with the normal hormonal balance, and evidence to this effect has been presented (2, 7). Although a disturbed endocrine picture might well explain the mechanism of caloric restriction in the inhibition of mammary tumors, it offers no solution as to the retardation of neoplasms induced with *hydrocarbons* or with *ultraviolet irradiation*. Furthermore, a decreased secretion of estrogens resulting from a deficient diet does not appear to be the only factor involved in decreasing the incidence of mammary tumors among mice kept on such diets. The administration of diethylstilbestrol to a group of cystine-deficient mice induced continuous estrus and stimulated development of the mammary glands, but the incidence of mammary tumors was increased from 0 to 45 per cent, only half the usual incidence found in the normal controls (7). It appears, therefore, that a lack of estrogen offers only a partial explanation even for the inhibition of a tumor arising in a gland whose normal function is closely interrelated with this hormone.

The influence of caloric restriction is unique among inhibitors of tumor genesis because of its effectiveness for such a variety of tumors. Calorie reduction has been shown to retard the formation of neoplasms that occur spontaneously or of those induced by chemical hydrocarbons or ultraviolet irradiation—in fact, its effect has been demonstrated for all tumor types for which adequate tests have been made (10, 11). Morris (7), however, indicates that the influence of caloric restriction is limited to only a few types of neoplasms. As evidence for his statement he cites work from our laboratory in which well nourished rats given an azo dye were more resistant to hepatic tumors than were rats on a poorer diet, but it should be pointed out that the experiments to which he refers have no bearing on the question of the effect of calorie reduction on hepatic tumors, owing to the fact that other variables were being studied. Nevertheless, it may be very difficult, if not impossible, to demonstrate the retarding effect of caloric restriction on the genesis of hepatic neoplasms, since this important organ appears to have first call on incoming nutrients.

The effectiveness of caloric restriction in retarding such a variety of tumor types in laboratory animals focuses attention as to its possible significance in man. Certain statistics obtained from life insurance records on the relation of weight and cancer incidence have been quoted as evidence that a correlation exists (3,

13). In general this information indicates that among people who were overweight at the time of issuance of the insurance policy there was a somewhat greater proportion of deaths from cancer than among persons of average weight or those who were underweight. The importance of this relationship is as yet unknown because there may be several factors that affect the development of obesity. Morris (7) suggests that too much emphasis cannot be placed on the available statistics of the type quoted, because the weight records were made many years prior to death from cancer. Although there may be many faults in the statistics as presented, actually one of their merits is that the comparison of cancer deaths was made with weight records obtained a number of years before the onset of cancer. Such weights give a better picture of the eating habits of a person when he is presumably in good health and during the time when a neoplasm may be in the earliest stage of formation, and it is at this period that the dietary influence would be expected to be most effective. Certainly little could be gained in comparing cancer mortality with the weight of patients at the time the neoplasm has attained a size large enough to present symptoms. The evidence from the present experiment and from other investigations (14) indicates that dietary restriction has little influence on the growth of large neoplasms.

Whether it will be practical or possible to prevent human cancer by dietary restriction is not possible to predict at the present time. To obtain data on this aspect of the problem would be a difficult task, and one that would extend over a period of many years. With the various food preferences and habits of people, any attempt to restrict the total intake and yet retain a well balanced nutritive diet would be no easy matter even under the supervision of a physician, to say nothing of the difficulties encountered if the task of selecting the proper food were left to the discretion of the person himself. There would be no advantage in reducing the incidence of one disease only to have others flourish. Perhaps, at the present time, the influence of dietary restriction could best be tested as a postoperation treatment in those who have had cancers surgically removed. If such a procedure were applied to patients in which all visible neoplastic tissue had been excised, a retardation of invisible metastases might result.

SUMMARY

Eight groups of 40 strain C mice each were placed on diets that varied in their content of calories, protein, and fat. Half of the groups were allowed a caloric intake of 9.3 calories per mouse per day, and the other half were restricted to 5.7 calories per mouse

per day. The groups were further divided in such manner that the level of protein was either high or medium, and the amount of fat either medium or low. After the mice had been stabilized on their diets for 50 days, each was injected subcutaneously with 200 μ gm. of 3,4-benzpyrene in 0.2 cc. of corn oil. A comparison was made between caloric consumption, tumor formation, and the level of blood sugar.

The mice on nonrestricted diets were heavier, the blood sugar tended to be higher than in those whose caloric intake was restricted, and the development of sarcomas was facilitated in the mice that were relatively hyperglycemic. Although the evidence indicates that under certain conditions the development of neoplasms is favored in animals with a somewhat elevated blood sugar, this in itself was not necessary for tumor formation as was shown in the case of mice receiving a high caloric diet in which considerable carbohydrate was replaced by protein and fat. In this case the incidence of sarcomas was high, although the blood-sugar level was not much different from that of the restricted mice.

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Certain Effects of Dietary Pyridoxine and Casein on the Carcinogenicity of *p*-Dimethylaminoazobenzene*

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Miner and his associates (11) studied the incidence of liver tumors in rats fed *p*-dimethylaminoazobenzene in synthetic diets containing 12 per cent of purified casein and various levels of the B vitamins. They observed that lowering the pyridoxine content of the diet from 2.5 to 0.2 mgm. per kgm. of diet decreased the incidence of hepatomas at 6 months from 67 per cent to 7 per cent. For a further test of this dietary effect Kline and his co-workers (4) inoculated rats and mice receiving high or low levels of pyridoxine with malignant tumors. In both species the number of takes, the percentage of regressions, and the size of the surviving neoplasms indicated that the diets low in pyridoxine retarded the growth of these tumors. Similar experiments by Bischoff, Ingraham, and Rupp (1) are in agreement with these observations. Kline and his group (4) further showed that the tumor incidence of mice painted with methylcholanthrene was 36 per cent on a low pyridoxine diet and 62 per cent when a high level of this vitamin was fed.

However, subsequent experiments in this laboratory have indicated that the effect of low levels of pyridoxine on the carcinogenicity of *p*-dimethylaminoazobenzene is more variable than the protection given by hydrogenated coconut oil (9, 10) or by high levels of riboflavin (3, 11). Furthermore, Miller and Baumann (6) showed that adult rats on diets free of pyridoxine survived much longer if they had received abundant supplies of pyridoxine during the period of growth than if only minimal amounts had been fed during this period. The present study was therefore designed to determine if the amount of pyridoxine fed to young rats would subsequently influence the formation of hepatic tumors due to *p*-dimethylaminoazobenzene on diets low in pyridoxine. Since pyridoxine or its deriva-

tives appear to be important in protein metabolism (2, 5, 7), both high and low levels of casein were fed with two levels of pyridoxine.

METHODS

Equal numbers of male and female albino rats of the Sprague-Dawley strain were raised from weaning on synthetic diets (Table I) containing either 1.5 or 6.0 mgm. of pyridoxine per kgm. The rats fed the high pyridoxine diet reached an average weight of

TABLE I: COMPOSITION OF DIETS

	For growth gm. per kgm.	For tumor induction gm. per kgm.
Purified casein (9)	180	120 or 480
Corn oil	50	50
Salts	40	40
Glucose monohydrate	730	790 or 430
<i>p</i> -Dimethylaminoazobenzene	—	0.6
	mgm. per kgm.	mgm. per kgm.
Pyridoxine hydrochloride	1.5 or 6.0	0.2 or 2.5
Thiamine hydrochloride	3.0	3.0
Nicotinic acid	3.0	—
Calcium pantothenate	13.0	7.0
Riboflavin	2.0	2.0
Choline chloride	1000.0	300.0

175 gm. in 8 weeks, while those receiving the lower level of this vitamin required 9 weeks to attain the same weight. At these times they were divided into groups of 15 to 17 members of comparable weight and sex, and fed several different diets (Table I) containing 0.06 per cent of *p*-dimethylaminoazobenzene. The quantities of vitamins in the latter diets were those previously found to permit the induction of liver tumors under our conditions (11), although higher levels of some of the vitamins were fed for the growth of the young rats. Of those raised on either the high or low pyridoxine diets, one group was given 0.2 mgm. and another 2.5 mgm. of pyridoxine per kgm. of a 12 per cent casein diet. In addition,

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two groups of the rats raised on the low pyridoxine diet were fed 48 per cent casein diets containing 0.2 or 2.5 mgm. of pyridoxine per kgm. The rats received 1 drop of halibut liver oil weekly during the growth period, and 1 drop monthly for the rest of the experiment. They were kept in groups of 5 to 8 in screen-bottomed cages, and food and water were given *ad libitum*. At 3 week intervals the amount of diet consumed by each group of rats was determined over a 3 day period.

The azo dye was incorporated in the diets by dissolving it in the fat with heat. The rations were mixed every 2 to 4 weeks and stored at 0° C. After the rats had been on the diets containing the azo dye for 120 days, their livers were examined by laparotomy and the animals were continued on the same diet as

EFFECT OF PYRIDOXINE FED DURING GROWTH

In each case the rats receiving the low pyridoxine diets with the carcinogen had fewer hepatomas than their controls, but the protection afforded by the low pyridoxine diets was much greater for rats that had received only minimal amounts of this vitamin prior to the dye. Thus those raised on the low level of pyridoxine and then fed the 12 per cent casein diets containing *p*-dimethylaminoazobenzene and 0.2 or 2.5 mgm. of pyridoxine per kgm. had tumor incidences of 19 and 60 per cent respectively at 4 months, and 50 and 87 per cent at 6 months (Groups 3 and 4). Of the rats raised on the high level of pyridoxine and subsequently fed the above diets, 19 and 41 per cent of those receiving 0.2 or 2.5 mgm. of pyridoxine respectively had neoplasms at 4 months, and 81 and

TABLE II: THE INCIDENCE OF HEPATIC TUMORS IN RATS RAISED AND MAINTAINED ON SYNTHETIC DIETS HIGH AND LOW IN PYRIDOXINE AND CASEIN

Group no.	Growth diet, Pyridoxine per kgm., mgm.	Maintenance diet *		Average weight increment at 4 mo., gm.	Average daily food intake,† gm. per rat	Survival ‡ at 4 mo.	Incidence § of tumors		Negative survivors at 6 mo.	Cirrhosis
		Pyridoxine per kgm., mgm.	Casein, per cent				4 mo.	6 mo.		
1	6.0	2.5	12	36	10.1	15/15	7/15	15/15	0	Moderate
2	6.0	0.2	12	—19	8.3	16/17	3/16	13/16	3	Mild
3	1.5	2.5	12	20	9.7	15/15	9/15	13/15	1	Moderate
4	1.5	0.2	12	—29	7.7	16/17	3/16	8/16	8	Mild
5	1.5	2.5	48	41	11.3	12/15	9/12	11/12	1	Mild
6	1.5	0.2	48	—43	7.6	14/17	0/14	1/14	10	Mild

* Contained 0.06 per cent *p*-dimethylaminoazobenzene for first 4 months.

† The average of 5 determinations at 3 week intervals of the food consumed over a 3 day period.

‡ Survival = number alive at end of 4 months over number at start.

§ Incidence = number with tumors over number of survivors at 4 months.

before, but minus the carcinogen, for an additional 60 days. The rats were then killed and a final examination of the livers was made.

RESULTS

The level of pyridoxine fed during the period of tumor induction was reflected by the health of the animals. The rats on the high pyridoxine diets (Table II, Groups 1, 3, and 5) ate about 10 gm. of food daily and gained 20 to 40 gm. during the dye-feeding period, whereas those receiving the low level of this vitamin (Table II, Groups 2, 4, and 6) ate only 8 gm. daily and lost 20 to 40 gm. in the first 4 months. It was necessary to supply each of these rats with 2 µgm. of pyridoxine every day by dropper during the ninth and 12th weeks, and to raise the pyridoxine content of the diets from 0.2 to 0.3 mgm. per kgm. during the 13th to 16th weeks. After feeding of the dye was stopped at 4 months it was possible to maintain the rats for the rest of the experiment with 0.2 mgm. per kgm. of diet.

100 per cent developed tumors by 6 months (Groups 1 and 2). Of these animals (Groups 1 to 4) the lowest tumor incidence was observed in Group 4; this group also consumed the least food. Similarly, the extent of cirrhosis in all the groups paralleled the number of neoplasms; it was mild in the groups fed the low level of pyridoxine and moderate in those given the higher level.

EFFECT OF LEVEL OF PROTEIN

A second factor that affected the carcinogenicity of *p*-dimethylaminoazobenzene in diets low in pyridoxine was the level of casein. This is seen by comparing the four groups of rats raised on the low level of pyridoxine. The rats fed 48 per cent of casein and the low level of pyridoxine (Group 6) had no tumors at 4 months and only 1 (7 per cent) was noted at 6 months, while the rats that received 12 per cent of casein and the same level of pyridoxine (Group 4) had an incidence of 19 and 50 per cent at 4 and 6 months respectively. Each of these groups consumed

approximately the same amount of food, and the livers were mildly cirrhotic. Most of the rats receiving 12 or 48 per cent of casein and the high level of pyridoxine (Groups 3 and 5) had hepatomas by 4 months; these incidences were comparable despite the higher food consumption and milder cirrhosis of Group 5.

DISCUSSION

These experiments demonstrate several facts that have both specific and general implications concerning the control of the formation of experimental tumors by dietary means. Specifically they illustrate the necessity of adequate amounts of pyridoxine for the genesis of tumors induced by *p*-dimethylaminoazobenzene. Of greater importance, perhaps, is the demonstration that the nutritional history of an animal can have a definite influence on the subsequent formation of hepatic neoplasms. It is possible that the level of other dietary ingredients fed during the growth period may have analogous effects, and variations in the results of similar experiments could be explained by the differences in the nutritional background of the animals employed. For instance, since large amounts of dietary riboflavin protect rats from liver tumors due to the azo dye (3, 11), animals with large stores of this vitamin might be more resistant to the carcinogen than those with minimal stores. It is apparent, therefore, that in any comparison of results among groups of rats obtained from different sources, it is important to consider the dietary history of the animals. The data also demonstrate that efficient tumor induction by *p*-dimethylaminoazobenzene is feasible in rats both raised and maintained on highly purified diets.

In an earlier study (6) adult rats that had been raised from weaning on diets containing high levels of pyridoxine were depleted of the vitamin less readily than those given less during the growth period. Similarly, in this series the animals fed the low pyridoxine growth diet prior to the low-pyridoxine:low-casein diet containing *p*-dimethylaminoazobenzene appeared to be more deficient than those fed the same azo dye diet but given more pyridoxine during the period of growth. This was evident from the smaller amounts of food consumed and the greater loss of weight of the rats raised on the low level of the vitamin. Accordingly, it is probable that the lower tumor incidence of the rats raised on the low-pyridoxine diet was due to their greater average degree of deficiency during the period of tumor induction and growth.

Several studies have indicated that pyridoxine is involved in protein metabolism. For example, the re-

quirement of mice for pyridoxine was found to be 3 to 4 times greater on 60 per cent of casein than when only 20 per cent was fed (7). Rats (5, 8) or mice (7) deficient in pyridoxine excreted 10 to 20 per cent of ingested *L*-tryptophan as xanthurenic acid, while practically none of this compound was excreted by control animals. Furthermore, pyridoxal stimulated greatly the decarboxylation of tyrosine by cell suspensions of *Streptococcus faecalis* R (2). The results of the present experiment also suggest a relationship between protein metabolism and pyridoxine. With adequate pyridoxine an increase in the level of casein in the diet from 12 to 48 per cent did not affect the tumor incidence; but when a low level of pyridoxine was fed, the rats receiving 48 per cent of casein developed fewer hepatomas than those on 12 per cent of casein. After 6 months only 1 of 14 rats on the high protein diet had developed a tumor, as compared to a 50 per cent incidence in the group on the lower level of casein. Since the metabolism of large amounts of casein appears to cause a more rapid depletion of the pyridoxine stores of rats, those fed the high-casein:low-pyridoxine diet were probably more deficient than those on the low-casein:low-pyridoxine diet. This would explain also the greater weight loss and poorer physical condition of the deficient rats on the high protein diet.

Although the amount of food eaten by the rats in each of the groups varied from 7.6 to 11.3 gm. per day, these differences apparently were not responsible for the effects observed. Of the rats receiving the azo dye in the low pyridoxine diets, those on the high and low levels of casein (Groups 4 and 6) ate approximately the same amount of food; yet the tumor incidences were 7 and 50 per cent respectively at 6 months. Further, while the daily food intakes of the groups fed the high level of pyridoxine differed by as much as 1.6 gm. the percentage of neoplasms in the three groups was very similar. These results are comparable to those observed in earlier studies (9, 10, 11), in which rats with the highest incidences of tumors have frequently consumed less diet and carcinogen than the protected animals.

The mechanism by which a lack of pyridoxine inhibits tumor formation has not been studied, but it seems possible that after the animals reach a certain state of deficiency they may be unable to utilize a sufficient amount of one or more amino acids for the synthesis of protein. In such a situation the synthesis of protein in both normal and neoplastic tissue could not proceed, which would account for the loss in weight and for the failure of tumor induction and growth.

SUMMARY

1. Weanling albino rats were raised for 8 to 9 weeks on synthetic diets containing 1.5 or 6.0 mgm. of pyridoxine per kgm. Groups of 15 to 17 were then fed 0.06 per cent of *p*-dimethylaminoazobenzene in synthetic diets containing 12 or 48 per cent of casein and 0.2 or 2.5 mgm. of pyridoxine per kgm. After 4 months the livers were examined by laparotomy; the rats were continued on the same diet without the dye for another 2 months, and were then killed for a final tumor count.

2. In each case the rats on the low pyridoxine diets containing the azo dye had fewer tumors than their controls receiving more of this vitamin. However, of the rats fed the low-pyridoxine:azo-dye diets those raised on the low pyridoxine diet had fewer hepatomas than the animals that received a higher level during the period of growth.

3. Substitution of 48 per cent of casein for the usual 12 per cent level in the low pyridoxine diets decreased the incidence of liver tumors from 50 to 7 per cent. When the rats received adequate pyridoxine the tumor incidence on 48 per cent of casein was equal to that on the 12 per cent casein diet.

4. The results demonstrated that the number of hepatomas induced on a given diet might be influenced by the nutritional history of the animals. Since high incidences of tumors were observed in rats raised and maintained on highly purified diets, such diets can be used in experiments where it is desirable to control the nutritional background.

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Phosphorus Compounds in Animal Tissues

II. The Nucleic Acid Content of Homologous Normal and Cancer Tissues*†

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The concept that nucleic acids are intimately associated with fundamental cellular processes has gained considerable favor within the last few years. This can undoubtedly be attributed to the researches of Caspersson and his associates. Caspersson, with the aid of ultraviolet spectrophotometry, has been able to measure the nucleic acids in various parts of the cell under a variety of experimental conditions. He has demonstrated, for example, that DNA¹ is found in certain portions of the chromosome and that its concentration undergoes cyclic changes, which can be correlated with mitosis (7). He has also been able to show that high concentrations of PNA¹ are found in the cytoplasm of cells actively engaged in protein synthesis, and in the cytoplasm of such rapidly growing tissues as embryos, and malignant tumors (6, 8-10).

The peculiar localization of DNA in the chromosomes led to the hypothesis that it is closely associated with, if not in fact identical with, the genes. A barrier to this idea has been the comparative simplicity of the structure of DNA in contrast to the wide variety of known genes. Nevertheless, the first direct experimental evidence in support of this hypothesis has now appeared. In a classical piece of work, Avery, MacLeod, and McCarty isolated a DNA from *Pneumococcus* Type III that was capable of inducing the transformation of *Pneumococcus* Type II into Type III (2).

These are only a few of the findings that could be cited to show the importance of nucleic acids in cellular physiology, but as the subject has been adequately reviewed (12, 15, 19, 20, 27, 31, 36) it need not be further considered here. The need for quantitative chemical analyses of homologous normal and cancer

tissues for each type of nucleic acid is apparent. It is the purpose of this paper to describe the application of chemical methods (34) to this problem.

METHODS

Measurement of nucleic acids.—DNA and PNA were measured by the diphenylamine, carbazole, and orcinol reactions on hot trichloroacetic acid extracts of tissues by methods which were described previously (34). The tissues were homogenized (32) and aliquots equivalent to the following fresh weights were used for analysis: liver and hepatoma, 200 mgm.; lung and lung tumor, 100 mgm.

Measurement of nucleotides and nucleosides.—An estimate of the amount of nucleosides and nucleotides in the tissues studied was obtained by measuring the pentose content of the cold trichloroacetic extracts of these tissues with the orcinol reaction (29). This is a valid measurement of these compounds because both nucleosides and nucleotides are soluble in trichloroacetic acid and contain the sugar, *d*-ribose, and because nucleic acids are not soluble in cold trichloroacetic acid to a measurable extent.

Preparation of tissues.—The normal tissues came from animals on the regular laboratory ration of mixed grains. The rat hepatomas were induced by feeding *p*-dimethylaminoazobenzene in a highly purified diet (30). The mouse lung tumor, the transplantable lung tumor F, originally obtained from Dr. H. B. Anderson (1), had been induced with 1,2,5,6-dibenzanthracene. The tissues from which phospholipids were not removed were excised under nembutal anesthesia (50 mg./kg.) and frozen in liquid air immediately upon extirpation; those extracted with fat solvents were obtained from animals killed by decapitation and were not frozen.

RESULTS

The results of the analyses are presented in Table I. Emphasis should be placed upon the excellent agreement between the phosphorus found in the extract

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† Some of the material presented in this paper was taken from a thesis submitted to the Graduate School of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

¹ For the sake of convenience and brevity, the following symbols will be employed: DNA and PNA = desoxyribose and ribose nucleic acids respectively.

and that calculated from the nucleic acids present, and on the agreement between the DNA revealed by the diphenylamine method and that demonstrated by the carbazole method. In all the analyses, however, there is a discrepancy between the nitrogen found in the trichloroacetic acid extract and that which could be accounted for by nucleic acids. The reason for this discrepancy is unknown.

is considerably lower than the PNA content of normal rat liver (average of 4 liver analyses: PNA = 467 mgm. per 100 gm. fresh tissue, as compared to 754 mgm. in the livers of rats on the grain diet; Table I).

The results are compared with those of other investigators in Table II. It is clear that the agreement is good.

Measurements of the pentose-containing compounds

TABLE I: NUCLEIC ACID CONTENT OF HOMOLOGOUS NORMAL AND TUMOR TISSUES

Tissue	No. of analyses	Milligrams per 100 gm. fresh tissue										DNA by carb. DNA by DPA
		PNA	DNA	PNA/DNA	N found	N calc. †	N calc. N found	P found	P calc. †	P calc. P found	N found P found	
Rat liver *	7	754	236	3.19	191	161	0.84	105	95	0.91	1.82	1.08
		657-	196-	2.67-	173-	145-	0.75-	92-	85-	0.81-	1.63-	1.02-
		910	264	4.64	234	179	0.90	127	106	0.99	2.06	1.24
Rat liver	4	834	213	3.91	98	100	1.02
		668-	198-	3.15-	83-	85-	0.94-
		1050	221	5.30	115	118	1.07
Rat hepatoma *	6	715	513	1.39	252	201	0.80	115	119	1.03	2.19	1.02
		560-	440-	1.15-	207-	164-	0.70-	103-	97-	0.93-	1.85-	0.96-
		787	583	1.97	307	222	0.94	132	131	1.11	2.69	1.12
Rat hepatoma	2	580	521	1.18	99	106	1.07
Mouse lung *	8	238	586	0.41	208	137	0.66	68	81	1.19	3.06	1.01
		194-	399-	0.36-	143-	94-	0.60-	38-	56-	0.97-	2.39-	0.90-
		330	879	0.48	283	201	0.71	100	118	1.47	4.02	1.11
Mouse lung tumor *	7	800	948	0.83	331	288	0.87	152	170	1.12	2.18	1.01
		622-	661-	0.73-	257-	212-	0.79-	120-	124-	1.03-	1.97-	0.95-
		900	1103	0.94	397	327	1.02	174	194	1.26	2.39	1.08

* In these analyses, the phospholipids were not extracted prior to the nucleic acid extraction.

† These calculations were made on the assumption that DNA contained 9.89% P and 16.76% N, and that PNA contained 9.5% P and 16.1% N.

TABLE II: COMPARISON OF THE PRESENT RESULTS WITH THOSE OF OTHER INVESTIGATORS

Tissue	Mgm. DNA per 100 gm. fresh tissue		Mgm. phosphorus per 100 gm.			
			Fresh tissue		Dry tissue	
	Present results	(27)	Present results	Previous results	Present results	Previous results
Normal rat liver	236	231.5	105	149 (13)	362	340 (3)
	213	222.2	98	227 (16)	338	505 (13)
				110 (25)		310 (14)
Rat hepatoma	513	444	115	128 (13)	600	535 (13)
	521		98	143 (13)	510	543 (13)
				149 (16)		490 (14)

The results show that the DNA content of both tumors and the PNA content of the lung tumor is considerably greater than that found in the homologous normal tissue. The PNA content of the hepatoma is slightly lower than that of the normal liver, however. It should be pointed out that the normal livers were obtained from rats kept on a grain diet, which cannot be compared with the carcinogenic diet. Preliminary results on the livers of rats maintained on the highly purified diet without *p*-dimethylaminoazobenzene for 17 weeks indicate that the PNA content of these livers

soluble in cold trichloroacetic acid gave the following results: normal rat liver, 152 mgm. pentose per 100 gm. fresh tissue; rat hepatoma, 55 mgm. pentose; mouse lung, 60 mgm. pentose; and mouse lung tumor F, 90 mgm. pentose.

Preliminary results of the measurement of acid soluble, lipid, nucleic acid, and protein phosphorus are presented in Table III. Rat hepatomas induced by feeding *p*-dimethylaminoazobenzene are compared with the livers from rats maintained on the same diet without the azo dye for 17 weeks. The results show

decreases in the acid soluble, lipid, and protein phosphorus content and an increased nucleic acid phosphorus content of the hepatoma as compared to the liver, although the total phosphorus content of the two tissues is about the same (liver=311.3; hepatoma=303.4). Further work will be required to determine whether these differences are significant and reproducible.

DISCUSSION

The results of Caspersson (8) suggest that malignant tumors contain high concentrations of PNA in the cytoplasm, while Koller (25) maintains that malignant tumors contain high concentrations of DNA in the nucleus. The latter view has been challenged by Dounce (16) on the ground that the isolated nuclei of hepatoma cells contain less DNA than those of liver cells. Stowell and Cooper (37), however, have found that the thymonucleic acid content per cell is about 10 per cent higher for epidermoid carcinomas than for normal human epidermis.

Measurements of nucleoprotein phosphorus in homologous normal and cancer tissues show conflicting

changes in the distribution of the two types of nucleic acid may have occurred. In fact, measurement of the two types with colorimetric methods shows striking differences between the homologous normal tissue and cancer: The DNA content of both tumors is much greater than that of the corresponding normal tissue, and the PNA content of lung tumor much greater than that of normal lung. The PNA content of hepatoma, however, is little different from that of normal liver. The latter observation confirms the results of Davidson and Waymouth (13), and seemed in opposition to the findings of Caspersson on single cells. In an attempt to reconcile these results with those of Caspersson, measurements of the cytoplasmic volume-nuclear volume ratios of rat liver and hepatoma were made by the method of Chalkley (11). The results were as follows:

	$\frac{\text{Cytoplasmic volume}}{\text{Nuclear volume}}$
Liver	5.85
Hepatoma	3.04

Since Biesele (4) has stated that both normal liver and hepatoma have the same size distribution of nuclear

TABLE III: ACID SOLUBLE, LIPID, NUCLEIC ACID, AND PROTEIN PHOSPHORUS CONTENT OF NORMAL RAT LIVER AND RAT HEPATOMAS

Tissue	Number of analyses	Mgm. phosphorus per 100 gm. fresh tissue			
		Acid-soluble	Lipid	Nucleic acid	Protein
Rat liver *	4	98.8 \pm 5.3	119.7 \pm 9.0	68.8 \pm 2.3	24.0 \pm 3.5
Rat hepatoma †	4	86.6 \pm 2.8	92.3 \pm 8.3	106.1 \pm 7.0	18.4 \pm 2.0

* Livers from rats on highly purified diet without azo dye for 17 weeks.

† Induced by feeding *p*-dimethylaminoazobenzene.

results. On a dry weight basis, there seems to be definite agreement as to an increase in nucleic acid phosphorus (Table II). On a fresh weight basis, however, there is either little difference between the nucleoprotein phosphorus of liver and hepatoma, or there is a smaller amount in the hepatoma. Still, it must be emphasized that the methods used by previous investigators for the determination of nucleoprotein phosphorus were often a measure of residual phosphorus rather than a true measure of nucleoprotein phosphorus, and that the results may represent appreciable amounts of other protein-bound phosphorus. Our results, on the other hand, were obtained by a method that separates nucleic acids from all other phosphorus-containing compounds. The results show little difference between the total nucleic acid phosphorus content of liver and hepatoma.

Measurements of nucleoprotein or of nucleic acid phosphorus always include two variables, DNA and PNA. Hence it is possible that although little or no difference is apparent between the total nucleic acid phosphorus of normal tissues and cancer, definite

volumes, these ratios can be interpreted only to mean that the cytoplasmic volume in the hepatoma is about one-half as great as that of the liver cell. The average liver nucleus occupies but about 6 per cent of the volume of the cell, and it therefore follows that per volume of tissue the hepatoma must have about twice as many cells as normal liver. With these factors in mind, we can put the following interpretation upon our data. The DNA content of the hepatoma nucleus is about the same as, or slightly greater than, that of the liver nucleus. The PNA concentration in the cytoplasm of the hepatoma cell is much greater than that in the normal liver cell. It seems possible that the same interpretation may apply to lung and lung tumor, although such an interpretation is not necessary to support and extend Caspersson's findings.

We may conclude that the presence of high concentrations of nucleic acids in tumor tissues is now fairly well established. It remains to be seen whether these high concentrations are a cause or a result of the neoplastic state. In this connection the work of Masayama and Yokoyama should be mentioned (28). These

workers found a striking increase in DNA long before any hepatomas appeared, a result that may be of questionable value, however, if the increase is due merely to an increase in the number of cells per volume of tissue.

A fundamental aspect of nucleic acid research that is of considerable importance to the cancer problem, yet has been almost entirely neglected, is the isolation and characterization of the nucleic acids from homologous normal and cancer tissues. Some years ago it was asserted that the DNA from tumors had a much lower nitrogen-phosphorus ratio than did nucleic acids from normal tissues (35, 39). Although this was disproved by a number of investigators (5, 24, 38) no attempt was made to characterize the nucleic acids completely. At the present time only thymus nucleic acid and yeast and liver ribonucleic acids have been characterized, and the need for characterization of other nucleic acids is therefore apparent. Since the amount of tumor, and hence of nucleic acid, available is usually small, perhaps the best approach to the characterization of the nucleic acids would be the development of microanalytical technics for measurement of the pentoses and the nitrogenous bases in the nucleic acids. Methods for the pentoses are available, and have been applied in the present study. Adequate methods are at hand for the measurement of purine nitrogen (18, 23), also, and it should be possible to adapt existing colorimetric reactions to the quantitative measurement of the pyrimidine bases (21, 22).

SUMMARY

1. The desoxypentose nucleic acid, the pentose nucleic acid, and the acid soluble pentose content of rat liver, rat hepatoma, mouse lung, and mouse lung tumor were determined.

2. The desoxypentose nucleic acid content of both tumors was much greater than that of the homologous normal tissues.

3. The pentose nucleic acid content of lung tumor was much greater than that of normal lung tissue, whereas the pentose nucleic acid content of liver and hepatoma was about the same.

4. The acid soluble, the lipid, and the protein phosphorus content of rat hepatomas was found to be less than that of livers from rats on the same diet without the carcinogen, whereas the nucleic acid phosphorus content of the hepatoma was higher than that of the liver.

5. These findings are discussed in relation to the observations of other investigators.

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Attempts to Localize Tumor Metastases in Long Bones by Mechanical Trauma*

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The medical literature contains many discussions dealing with the influence of trauma on tumor development and numerous reports indicating that in some unexplained manner trauma may be a significant factor in initiating malignant growth, but relatively few articles concerning the influence of trauma on the localization of metastases. Toth (5), who studied 2 patients with generalized carcinomatosis to determine the influence of various mechanical injuries on the formation of metastases, was unable to demonstrate any definite causal relationship (see this article for further references). Lubarsch (4) could not localize metastases in tumor-bearing mice by fracturing bones whereas Ewing (1), on the other hand, cited 5 instances of localization at sites of trauma. Foulds (2), in a critical review on filterable tumors of fowls, stated that in fowls bearing Fujinami sarcoma, secondary growths have been induced by the injection of kieselguhr, lycopodium, powdered charcoal, etc. He also mentioned that, following intravenous injections of filtrates of Rous sarcoma I, tumor formation has been induced at the sites of injection of Scharlach R, tar, embryonic tissues, kieselguhr, histamine, and at points of injury. Jones and Rous (3) were able successfully to transplant a mouse tumor intraperitoneally only after preliminary irritations of the peritoneum by injections of lycopodium, and believed that this irritation was an important factor in causing localization of the tumor.

In view of the conflicting evidence and because of the importance of this problem from the medicolegal standpoint, the following experimental study was undertaken to ascertain whether or not trauma applied to long bones might be influential in the localization of metastases from a transplanted malignant tumor.

The Brown-Pearce rabbit tumor was used throughout this study. This is a highly malignant tumor, readily transplantable into the testes, from which it metastasizes early and, within 3 to 6 weeks from the

time of intratesticular transplantation, produces a generalized carcinomatosis.

Attempts were made to localize metastases in long bones by a single mechanical trauma and by chronic irritation. Bone metastases have not been observed in our stock tumor rabbits except in the spinal column, and then but rarely.

However, in order to ascertain whether or not the Brown-Pearce carcinoma grows in long bones, transplants were made directly into the femur in 6 normal male rabbits. The tumor grew well within the marrow spaces in all, soon invaded the periosteum and adjacent muscles, and metastasized extensively.

Trauma to the bones was produced by simple fracture of the humerus. In a series of 21 rabbits the left humerus was fractured and immediately afterward an intravenous injection of a suspension of tumor cells was made into the ear vein. In a second series of 12 rabbits the left humerus was fractured and 14 days later a suspension of tumor cells was injected intravenously into the ear vein. In a third series of 12 animals, tumor was transplanted into the testes (for technic, see *Am. J. Cancer*, 33:239-295, 1938). Two weeks later, after the testicular tumor was easily palpable, the left humerus was fractured.

Intravenous transplantation was done by the following technic: Portions of fresh sterile tumor tissue were crushed in a tissue press and passed through a fine sieve. The resultant jelly-like mass was then vigorously shaken for 10 minutes in saline and allowed to stand in a vertical position for 10 minutes. The larger particles of tumor quickly settled to the bottom of the flask and the supernatant fluid, consisting of fine particles of tumor suspended in saline, was separated. Ten cubic centimeters of this supernatant fluid was injected into the marginal ear vein of each rabbit.

It may be stressed here that the number of rabbits listed embraces only those which at autopsy disclosed metastases in the various organs, and which obviously died as a result of widespread metastases.

Roentgenograms of the entire skeleton of each rabbit were made after death. At autopsy, in those animals that had received the intravenous transplantation,

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most of the metastases were found in the lung, but the kidneys and liver were also involved. The animals in which the tumor was transplanted into the testes showed metastases principally in the inguinal lymph nodes, liver, and kidneys. The region of the fracture was carefully examined by means of roentgenograms in the gross, and a number of blocks were taken from the region of the fracture and the adjacent bone and soft tissue. There was no macroscopic evidence of tumor in this location. The histological examination disclosed tremendous cellular proliferation in the region of the fracture and callus formation, which varied according to the interval between the time of fracture and the death of the animal. In several cases serial sections were cut from the region of the fracture, but in not a single instance were tumor cells encountered.

The second set of experiments was undertaken to determine the influence of chronic mechanical irritation on the possible localization of tumor metastases. To produce such an irritation, a rough piece of a small vitallium screw was placed immediately beneath the periosteum in close contact with the cortex of the distal end of the femur beneath the quadriceps tendon, and held in position by silk sutures. The vitallium screw was placed so that with each movement of the leg the metal rubbed against the bone. In every instance the correct position of the screw was verified by roentgenograms. These experiments were divided into two parts. In the first series 23 animals were used. Six weeks after the vitallium screw had been placed in position, a testicular transplantation of the tumor was made. In the second series (11 animals), intravenous transplantation of tumor cells was done 6 weeks after the vitallium screw had been placed. Again, only

those animals that obviously died as a result of a widespread tumor growth are mentioned in this report.

After the animal had died, the position of the screw was studied once more by means of roentgenograms. A thickened periosteum, evidence of mechanical irritation, was almost invariably noted, and again widespread metastases were recorded. In the region of the vitallium screw, the periosteum was greatly thickened and firm, but no gross evidence of tumor was encountered. Multiple sections were taken from the bone in the area of the thickened periosteum and both periosteum and bone were submitted to careful histologic study, but in no case were tumor cells encountered at the site of the mechanical irritation.

SUMMARY

Mechanical trauma or chronic irritation of bones played no role in the localization of metastases from transplanted Brown-Pearce carcinomas in rabbits.

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Reticuloendothelial Immune Serum (REIS)

III. The Effect of Strong Concentrations on the Growth of Walker Rat Sarcoma 319 *in vitro*

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(Received for publication July 10, 1945)

The importance of the reticuloendothelial system in relation to neoplasms has been recently brought into focus by a group of Soviet workers. According to Shimkin (18), blockading of the reticuloendothelial system has been used by Roskin (16) as a means of growing heteroplastic tumors. Bogomolets (3) has reported the effect of specific antireticular cytotoxic serum (ACS) on the genesis, survival, and metastasis of cancer. Anti-human spleen horse serum has been shown (9) to increase the carcinolytic capacity of the serum of cancer patients.

According to Bogomolets (4) "Whereas the macrophages penetrating the tumor tissue destroy the carcinogenetic cellular element, the fibroblasts and microphages form a strong line of demarcation around the cancerous foci." It is believed that this activity, along with the production of trephone-like substances by macrophages, assists in the resistance against cancerous proliferations. Bogomolets and Neuman found that at very low concentrations anticytotoxic serum was capable of reducing the number of positive inoculations of tumor grafts; the reverse was true with high concentrations. Bogomolets (4) states that, "... Dr. Neuman showed that stimulation of the connective tissue with anti-reticular cytotoxic serum in many cases leads to complete disappearance of large carcinogenous tumors in mice and decreases the number of metastases of the cancer to the lungs." Disappearance of pain, and of metastases in lymph nodes are given as evidence of the value of such sera in inoperable human cancer.

Research in our laboratories has corroborated the statement by Soviet workers that reticuloendothelial

immune serum (REIS) prepared according to the method described by Marchuk (11) has both damaging properties and stimulating action. Thus homologous sera, when incorporated in the culture medium at high concentration, have been shown to restrict the outgrowth of splenic fragments and cause cell clumping (14), as well as total inhibition of heart fragments (15). Moreover, this effect was demonstrated *in vivo* by the experimental production of bartonellosis in latent carriers (1, 2). Preliminary experiments suggest that low concentrations of homologous sera stimulate the migration of cells from chick heart explants (13). These effects appear to be species specific, since they could not be produced by antisera made from antigen derived from a different species of animal.

MATERIALS AND METHODS

Walker rat sarcoma 319 was selected for a study of the effect of REIS on malignant tissue because its distinct cultural characters *in vitro* make it easy to distinguish it from other tumors and from normal tissues (10). Moreover, the metabolism of pure cultures of these cells has been carefully studied by Victor and Lewis (19) and by Gemmill, Gey, and Austrian (7). We are indebted to Dr. George O. Gey, of the Johns Hopkins Medical School, for his kindness in supplying us with a strain of Walker rat sarcoma 319.

All the results herein reported were conducted in hanging drop preparations. At least 8 slides were used for each experimental condition. The medium consisted of 50 per cent heparinized rooster plasma, 12.5 per cent extract from chick embryos incubated

DESCRIPTION OF FIGURES 1 TO 6

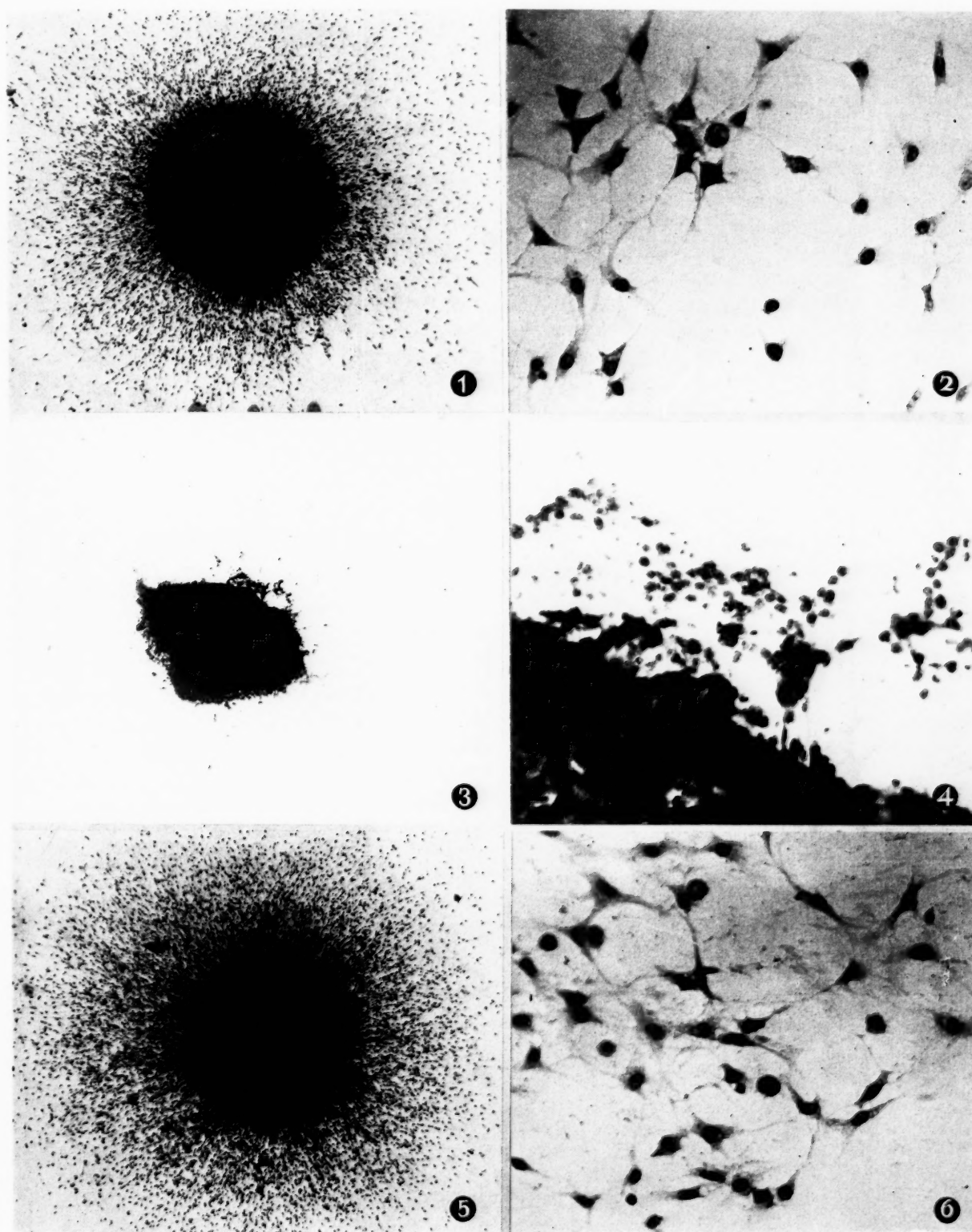
All are of Walker rat sarcoma 319. Figs. 1, 3, and 5 represent a magnification of 34 diameters, while Figs. 2, 4, and 6 for corresponding cultures were taken at approximately 315 \times .

Figs. 1 and 2.—Control cultures cultivated in medium containing a 1:4 dilution of normal rabbit serum.

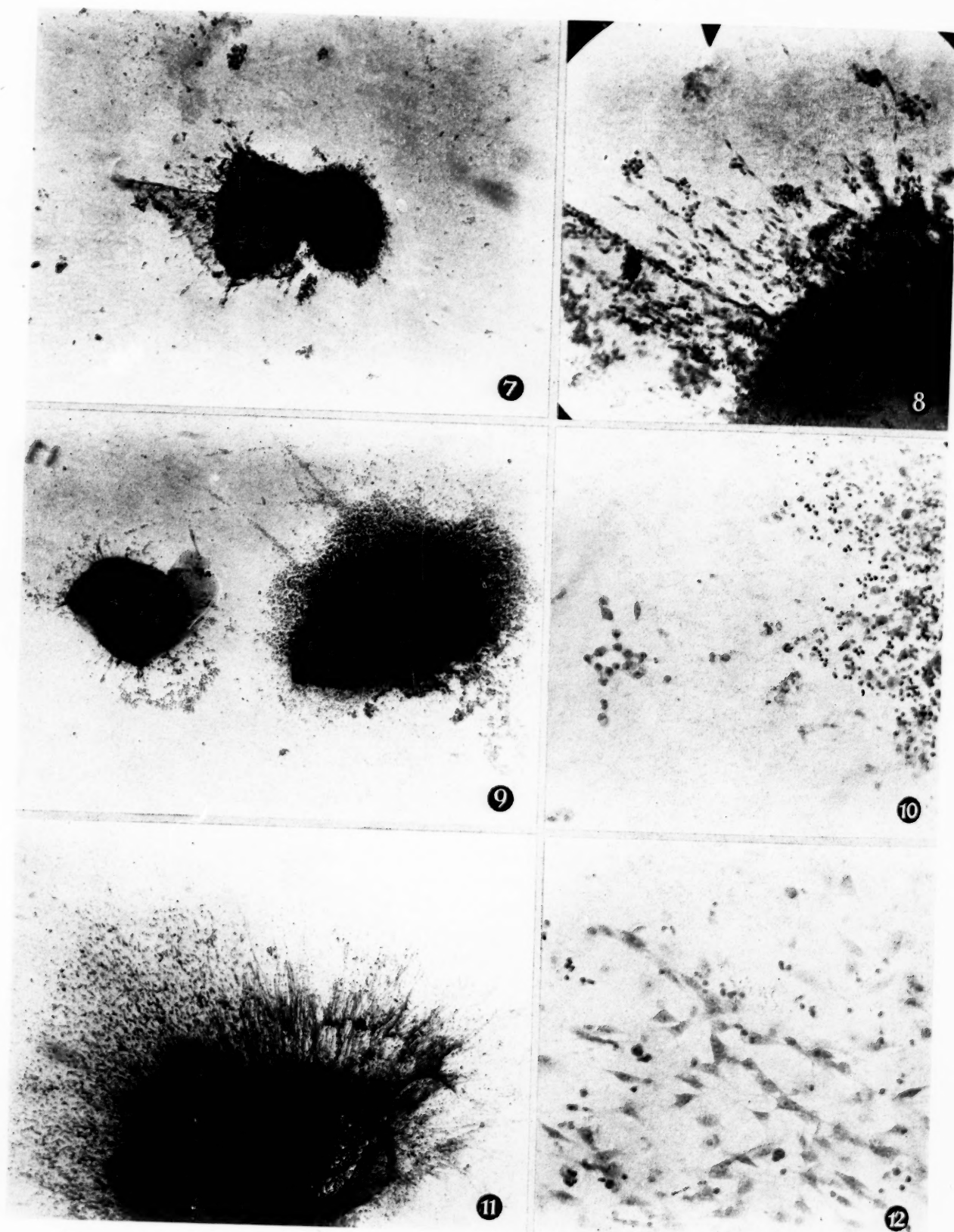
Figs. 3 and 4.—Culture containing a 1:4 dilution of anti-

spleen rat REIS (homologous). Note rounded and pycnotic cells in Fig. 4.

Figs. 5 and 6.—Culture containing a 1:4 dilution of anti-spleen chick REIS (heterologous).



FIGS. 1-6



FIGS. 7-12

6 to 10 days, 12.5 per cent rat serum, and 25 per cent REIS at various concentrations. Controls consisted of identical materials, but normal rabbit serum was substituted for the REIS.

The REIS used was rat anti-spleen serum with a complement-fixation titer of 1:1,600 and chick anti-spleen and bone marrow serum with a titer of 1:1,200.

Tumor tissue was used either alone or in combination with fragments of spleen from newborn rats. Cultures were incubated at 37.5° C. for 3 to 5 days and fixed in 10 per cent formalin in saline. Harris hematoxylin and toluidin blue were used for staining.

RESULTS

In the first series of experiments, homologous (anti-rat) and heterologous (anti-chick) sera were incorporated in the media at high concentration. Clots contained 25 per cent of the undiluted serum; this is reported as a dilution of 1:4. Results were consistent in showing almost total inhibition in the migration of malignant cells from explants in the presence of anti-rat serum (Fig. 3). Moreover, small clusters of cells immediately adjacent to the explants were rounded and pycnotic (Fig. 4). In contrast to these results, explants in medium with anti-chick sera showed outgrowths (Figs. 5, 6) typical of control cultures containing normal rabbit serum (Figs. 1, 2). These findings were obtained in 16 cultures representing each experimental condition, proving the species specificity of REIS.

Since antisera are prepared against an antigen consisting of splenic cells it was decided to conduct experiments with homologous REIS at various concentrations in conjunction with the spleen of newborn rats alone and in combination with fragments of tumor tissue. Outgrowth from Walker rat sarcoma was almost totally inhibited by REIS at 1:4, but results at 1:16 and 1:64 proved roughly comparable to controls. In contrast, migrating cells from splenic fragments were reduced in number and showed clumping (14) at 1:4, 1:16, 1:64, 1:128, and 1:256; but at 1:512 the

results resembled those obtained in control cultures. Inhibition of the sarcoma cells at high concentration shows the overlapping specificity of REIS, while the injurious effects observed in spleen grown with considerably greater dilution of REIS demonstrates specificity of the antiserum when used against the type of cells originally employed as antigen.

Cultures in which both tumor and splenic cells were introduced into the clot (conjoint cultures) proved especially interesting. Controls containing no REIS, but in which 25 per cent normal rabbit serum was included, showed excellent growth and mixture of both species of cells (Figs. 11, 12). In media containing REIS as well as splenic fragments in addition to the sarcoma cells, inhibition was observed at all concentrations at which spleen alone was affected. That is, in the presence of spleen, sarcoma cells, which were not injured when cultivated in a medium with a 1:16 dilution of REIS, were found to be rounded and clumped in the presence of as little as 1:256 of the homologous REIS (Figs. 6, 7, 8, 9). Outgrowth of both the tumor and spleen fragments appeared normal with 1:512 REIS. It would seem, therefore, that in the presence of splenic elements, sarcoma cells were more susceptible *in vitro* to weaker concentrations of REIS than when cultivated alone.

DISCUSSION

In a recent paper Hungate and Snider (8) have reviewed and given additional experimental evidence for the capacity of living splenic cells to inhibit the growth of tumor tissues in chick eggs. Previous tumor immunization of hens and young pullets whose spleens were used against the tumors injected into eggs was not found to influence the results.

Workers in this field have tended to look upon the egg as a simple culture medium, and perhaps have not given sufficient consideration to immune responses of the living chick to splenic injections.

In an excellent contribution, Burke, Sullivan, Petersen, and Weed (5) have given experimental evidence

DESCRIPTION OF FIGURES 7 TO 12

Growth of spleen from newborn rats in conjoint culture with fragments of Walker rat sarcoma 319 under various experimental conditions. The magnification of Figs. 7, 9, and 11 is 26×, while corresponding high power photomicrographs were taken at approximately 229 diameters.

Figs. 7 and 8.—Inhibition of outgrowth in presence of a 1:128 dilution of anti-rat REIS. An enlargement of a portion of the tumor fragment (left side of Fig. 7) is shown in Fig. 8. Note clumps of splenic elements and bipolar sarcomatous cells.

Figs. 9 and 10.—Inhibition of outgrowth in presence of a 1:256 dilution of anti-rat REIS. Note considerably greater amount of cellular migration from explants. A group of cells lying between tumor (left) and spleen (right), which can be seen in Fig. 9, is represented at high magnification in Fig. 10.

Sarcoma cells can still be recognized, but their cytoplasmic processes are considerably withdrawn.

Figs. 11 and 12.—Luxuriant growth of both tumor (left) and spleen (right) can be seen in Fig. 11. Note mesenchymatous outgrowth from spleen. At higher magnification (Fig. 12) multipolar cells characteristic of Walker rat sarcoma 319 can be seen in association with wandering cells from the splenic explant.

for changes in organ antigenicity during ontogeny. Splenic cells from chickens 4 months to 1 year of age are certainly antigenic and unquestionably provide antibody formation in chicks by the 17th day. It appears, therefore, that such procedures may produce immune factors similar to those reported by Soviet workers and confirmed by us in studies on REIS.

In the preparation of antigen according to the method of Marchuk (11) spleen and bone marrow are ground in a mortar and centrifuged at 1,000 r.p.m. for 4 minutes. The resulting supernatant, which is injected into an antibody-forming host, contains intact cells. This fact is significant in the light of agreement between Murphy (12), Danchakoff (6), and Hungate and Snider (8) that cells are the agent essential for inhibition of tumor in eggs. But Stevenson (17), on the other hand, reported that tumor grafts and spleen fragments grew vigorously side by side in the egg.

Marchuk (11) wrote that frozen antigens produced immune sera of significantly lower titer than fresh ones. Refrigeration has also been found to lower the effectiveness of spleen in inhibiting tumors in eggs (8).

Sarcoma cells grown *in vitro* in intimate contact with splenic elements were not inhibited, but in the presence of REIS damaging effects were noted at concentrations not injurious to sarcoma cells cultivated in the absence of spleen fragments. It seems likely that in the inhibition of tumor grown in eggs the splenic cells that are added may exert their effect in association with an anti-spleen immune body progressively developed by the living chick. According to Danchakoff (6) it is essential to bring both tumor and splenic cells into intimate association to insure the inhibitory effect. Results obtained thus far in tissue culture offer no contradiction to this possibility, but argue for the presence of REIS to insure the effect.

CONCLUSIONS

Cells of Walker rat sarcoma 319 were inhibited *in vitro* by homologous (anti-rat) REIS, but not by heterologous (anti-chick) REIS at similar concentrations.

By the use of an anti-rat REIS with a complement-fixation titer of 1:1,600 sarcoma cells were inhibited at a concentration of 1:4 but not of 1:16. Splenic cells were clumped and limited in migration by concentrations up to 1:256, but not at 1:512. Outgrowth of tumor was reduced when splenic cells were included in the medium, but this effect was not found for controls containing no REIS.

It is suggested that the inhibitory action of spleen on tumor cells is exerted in the presence of relatively strong concentrations of REIS. These observations may explain the results reported for the inhibition of

tumor in eggs by spleen; in such cases the injected spleen may cause the developing chick to produce the necessary REIS factor.

ACKNOWLEDGMENT

It is a pleasure to acknowledge indispensable technical assistance from Mrs. Madeline Lay in the preparation of tissue cultures.

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Abstracts

Reports of Research

A System of Grading Carcinogenic Potency.

BERENBLUM, I. [Oxford Univ. Research Centre of Brit. Emp. Cancer Campaign, Oxford, England] *Cancer Research*, 5:561-564. 1945.

A distinction is made between methods for evaluating carcinogenic response (designed for the detection of minor differences of response under controlled biological conditions) and a system of grading carcinogenic potency (aiming at approximation rather than precision, and applicable retrospectively to most of the existing data in the literature, irrespective of the methods employed). The system of grading described in this paper is sufficiently simple and flexible to allow such comparisons to be made for the whole range of carcinogens from the weakest to the strongest. It is based on the average carcinogenic induction time (or its equivalent), and includes a simple method of approximation for those weak carcinogens that produce very few tumors. The grading is then read off from a graph (or, alternatively, calculated from an appropriate formula), the system allowing for 12 grades of potency. The grading of 15 representative carcinogens by this system is included in an appendix.—Author's abstract.

The Biological Assay of Carcinogens.

LEA, D. E. [Strangeways Lab., Cambridge, England] *Cancer Research*, 5:633-640. 1945.

It is proposed that the mean of the logarithms of the induction times should be used as a means of summarizing the results of experiments in which a carcinogen is applied to a batch of animals, and some or all get tumors. The method of maximum likelihood is used to estimate this mean in experiments in which some of the animals die without tumors. A table is provided to facilitate the numerical work, and an example is worked out in detail.—Author's abstract.

Studies in Carcinogenesis with Azo Compounds.

I. The Action of Four Azo Dyes in Mixed and Pure Strain Mice. KIRBY, A. H. M. [Glasgow Roy. Cancer Hosp., Glasgow, Scotland] *Cancer Research*, 5:673-682. 1945.

Stock mice injected subcutaneously with 2'-amino-4,5'-azotoluene in olive oil solution, up to 472 days and a total dosage of 67.5 mgm., developed no neoplastic lesions. Similar mice injected subcutaneously with *p*-aminoazobenzene in arachis oil solution, up to 626 days with a total dosage of 192.5 mgm., developed no tumors at any site, either on an adequate diet or on a diet restricted in protein and probably in riboflavin. 4'-Amino-2,3'-azotoluene and N,N-dimethyl-*p*-aminoazobenzene have been injected subcutaneously in arachis oil solution into stock mice, Cba mice, and C57 black mice of both sexes. Hepatoma was induced with either dye in mice of either sex of all

3 genetic types (except male stock mice receiving the latter dye). Sarcoma at the site of injection was rare in stock and C57 black mice and was never seen in Cba mice. Lung adenoma was found in only 1 female stock mouse. Hemangioendothelioma was found in a few stock and C57 black mice; simple hemangioma also was found.

In mice of mixed origin and also in mice of the Cba and C57 black strains, 4'-amino-2,3'-azotoluene proved much more carcinogenic for the liver than N,N-dimethyl-*p*-aminoazobenzene, when administered in oily solution by the subcutaneous route. No sex difference in susceptibility was observed either in stock mice or in Cba mice with these latter dyes, or in C57 black mice with 4'-amino-2,3'-azotoluene; liver tumors were obtained in female C57 black mice, and not in males, with N,N-dimethyl-*p*-aminoazobenzene.—Author's summary.

Studies in Carcinogenesis with Azo Compounds.

II. The Action of Azo Compounds in Mice, and the Bearing Thereof on Theories of Azo Dye Carcinogenesis. KIRBY, A. H. M. [Glasgow Roy. Cancer Hosp., Glasgow, Scotland] *Cancer Research*, 5:683-697. 1945.

The investigations into the action of azo compounds in mice, reported in the literature, are reviewed from the points of view of the azo compounds used, the lesions evoked, and the strains of mice employed. The relative carcinogenicities of N,N-dimethyl-*p*-aminoazobenzene and 4'-amino-2,3'-azotoluene are shown to be reversed in mice as compared with rats. Theories explaining the order of carcinogenicities in one species will not suffice for the other species. The predominance of cholangioma in the livers of mice receiving azonaphthalenes and other data for rats and mice may indicate that metabolism of azo compounds to "benzidine type" derivatives favors bile duct proliferation, while "reductive fission" favors hepatoma formation.—Author's summary.

Effect of a Carcinogenic Hydrocarbon on Manifest Malignant Tumors in Mice. Eradication of Transplanted Leukemia in Mice and Attempts at Inhibition of Other Manifest Malignant Tumors in Mice by Treatment with 9:10-Dimethyl-1:2-Benzanthracene. STAMER, S. *Acta path. et microbiol. Scandinar.*, 47:1-158. 1943. From abstr. in *Biol. Abstr.*, 19:1404. 1945.

It has been claimed by a number of workers that carcinogenic hydrocarbons are capable of exerting an inhibitory effect on tumors of various kinds—transplanted tumors, spontaneous tumors, tumors induced by carcinogenic hydrocarbons, and transplanted tumors originally induced by carcinogenic hydrocarbons. A similar inhibitory effect has also been claimed for noncarcinogenic

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but related hydrocarbons. The author reviews this work and concludes that the inhibitory effect is doubtful, particularly because most workers have failed to take into account the weight loss occurring in the animals receiving carcinogenic hydrocarbons, although it is well known that loss of body weight itself may inhibit the growth of tumors, both transplanted and spontaneous. He has carried out a very extensive series of experiments, using 3 strains of mice and a variety of transplanted tumors (Crocker sarcoma 180, Street sarcoma, mammary carcinoma, squamous cell epithelioma, and leukemic tissue). The hydrocarbon used was 9,10-dimethyl-1,2-benzanthracene, given orally, intraperitoneally, and intravenously. When due allowance was made for loss of body weight due to administration of the carcinogen, no inhibitory effect could be demonstrated except in the case of transplanted leukemia in 1 strain of mice in which the hydrocarbon was given intravenously. The effect on transplanted leukemia depended on dosage: a total dose of 7.5 mgm. was sufficient to inhibit and cure the condition, the animals being alive 5 months later. The injections of carcinogenic hydrocarbon were begun on the same day as transplantation of the leukemic material and repeated 1, 2, 6, and 8 days later (1.5 mgm. doses). The injections had no toxic effect on the mice, and there was no evidence that subsequent new growths resulted. It is suggested that the possible therapeutic value of the hydrocarbon should be investigated in man.—M. H. P.

On the Absence of a Connexion between the Growth Retardation Produced by Polycyclic Aromatic Hydrocarbons and Sulphur Metabolism. WARREN, F. L., ELSON, L. A., and GOULDEN, F. *Biochem. J.*, **39**:xiv. 1945.

White *et al.* (*J. Biol. Chem.*, **131**:149. 1939) concluded that the retardation of growth produced in young rats by administration of such polycyclic aromatic hydrocarbons as 3,4-benzpyrene, methylcholanthrene, or pyrene was due to deprivation of sulfur-containing amino acids. They assumed that such sulfur-containing acids were necessary for detoxication by mercapturic acid formation. To test this hypothesis the urinary sulfur partition in rats injected with benzene, naphthalene, phenanthrene, anthracene, 1,2-benzanthracene, 1,2,5,6-dibenzanthracene, 3,4-benzpyrene, pyrene, or chrysene was examined. The effects of these hydrocarbons on the growth rates were also observed. No evidence of the excretion of mercapturic acids by rats treated with the carcinogens 3,4-benzpyrene and 1,2,5,6-dibenzanthracene was found. The retardation of growth (amounting to complete cessation in these experiments) produced by these hydrocarbons cannot be attributed to a deprivation of sulfur-containing amino acids.—E. L. K.

Certain Effects of Egg White and Biotin on the Carcinogenicity of *p*-Dimethylaminoazobenzene in Rats Fed a Sub-Protective Level of Riboflavin. KLINE, B. E., MILLER, J. A., and RUSCH, H. P. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Cancer Research*, **5**:641-643. 1945.

Six groups of 15 rats each were fed 0.06% of *p*-dimethylaminoazobenzene in highly purified diets containing a sub-protective level of riboflavin, *i.e.* 2 μ gm./gm. diet, and 12% of protein as vitamin-free casein, unheated dried

egg white, or heated dried egg white. Each rat of one group fed unheated egg white also received 2 μ gm. of crystalline biotin by subcutaneous injection 3 times a week. The dye was fed for 4 months and followed by the dye-free basal diets for another 2 months. The livers were inspected by laparotomy at 4 months and a final tumor count was made at 6 months.

The incidence of liver tumors at 6 months on the casein diets was 77 and 82%, while on the egg white diets it varied from 0 to 18%. Thus neither the injection of biotin nor the heat denaturation of the avidin present in the egg white destroyed the protective effect exerted by this protein. Biotin deficiency symptoms developed after 3 months on the unheated dried egg white diets, but did not appear when biotin was given or if the egg white was heated. The protection against hepatoma formation offered by egg white in these experiments appeared to be independent of any obvious biotin-egg-white relationship. It is important to note that these experiments were performed with diets containing a sub-protective level of riboflavin; the previous reports on the cocarcinogenic effect of biotin concerned diets containing highly protective levels of this vitamin.—Authors' abstract.

Certain Effects of Dietary Pyridoxine and Casein on the Carcinogenicity of *p*-Dimethylaminoazobenzene. MILLER, E. C., BAUMANN, C. A., and RUSCH, H. P. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Cancer Research*, **5**:713-716. 1945.

Weanling albino rats were grown for 8 to 9 weeks on synthetic diets containing 1.5 or 6.0 mgm. of pyridoxine per kgm. Groups of 15 to 17 animals were then fed 0.06% of *p*-dimethylaminoazobenzene in synthetic diets containing 12 or 48% of casein and 0.2 or 2.5 mgm. of pyridoxine per kgm. After 4 months the livers were examined by laparotomy; the rats were continued on the same diet without the dye for another 2 months, and were then killed for a final tumor count. In each case the rats on the low pyridoxine diets containing the azo dye had fewer tumors than their controls receiving more of this vitamin. However, of the rats fed the low pyridoxine-azo dye diets those raised on the low pyridoxine diet had fewer hepatomas than did the animals that received a higher level during the period of growth. Substitution of 48% of casein for the usual 12% level in the low pyridoxine diets decreased the incidence of liver tumors from 50 to 7%. When the rats received adequate pyridoxine the tumor incidence on 48% of casein was equal to that on the 12% casein diet. The results demonstrated that the number of hepatomas induced on a given diet might be influenced by the nutritional history of the animals. Since high incidences of tumors were observed in rats grown and maintained on highly purified diets, such diets can be used in experiments in which it is desirable to control the nutritional background.—Authors' abstract.

The Relationship of Caloric Intake and of Blood Sugar to Sarcogenesis in Mice. RUSCH, H. P., JOHNSON, R. O., and KLINE, B. E. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Cancer Research*, **5**:705-712. 1945.

Eight groups of 40 strain C mice each were placed on diets that varied as to the content of calories, protein, and

fat. Half of the groups were allowed a caloric intake of 9.3 calories per mouse per day and the other half were restricted to 5.7 calories per mouse per day. The groups were further divided in such manner that the level of protein was either high or medium and the amount of fat was either medium or low. After the mice had been stabilized on their diets for 50 days, each was injected subcutaneously with 200 µgm. of 3,4-benzpyrene in 0.2 cc. of corn oil. A comparison was made of caloric consumption, tumor formation, and the level of blood sugar. The mice on nonrestricted diets were heavier, the blood sugar tended to be higher than in mice whose caloric intake was restricted, and the development of sarcomas was facilitated in the mice that were relatively hyperglycemic. Although the evidence indicates that under certain conditions the development of neoplasms is favored in animals having a somewhat elevated blood sugar, this in itself was not necessary for tumor formation, as was shown in the case of mice receiving a high caloric diet in which considerable carbohydrate was replaced by protein and fat. In this case the incidence of sarcomas was high, although the blood sugar level was not much different from that of the restricted mice.—Authors' abstract.

The Dependence of Tumor Formation on the Degree of Caloric Restriction. TANNENBAUM, A. [Michael Reese Hosp., Chicago, Ill.] *Cancer Research*, 5:609-615. 1945.

The effect of different levels of caloric intake—from *ad libitum* down to approximately 60% of *ad libitum*—on the formation of spontaneous mammary and induced skin tumors in dba mice was studied by reducing only the amount of carbohydrate in the diet, while maintaining constant amounts of protein, fat, vitamins, and minerals (caloric restriction *per se*). Using as criteria both the incidence of tumors and the average time at which these appeared, it was found that inhibition of tumor formation is dependent on the degree of caloric restriction: Any degree of caloric restriction may exert some inhibitory effect on the formation of tumors and the lower the caloric intake the greater the inhibition. In the experiment on induced skin tumors there was a progressive increase in the mean time of appearance (latent period) as the caloric level was decreased. It is probable that the curve expressing the relationship between tumor incidence and caloric intake has a modified J shape; the ratio of the decrease in incidence to the decrease in caloric intake is greater in a particular caloric range.—Author's abstract.

The Dependence of Tumor Formation on the Composition of the Calorie-Restricted Diet as Well as on the Degree of Restriction. TANNENBAUM, A. [Michael Reese Hosp., Chicago, Ill.] *Cancer Research*, 5:616-625. 1945.

The inhibitory effect of caloric restriction on the formation of tumors in mice has been shown to be dependent on the actual degree of caloric restriction. The present experiments, which employed the spontaneous mammary tumor of the dba and C3H strain and the induced skin tumor, were performed to confirm this finding and also to ascertain the significance of the composition of the diet at various levels of caloric restriction. Three types of restricted diets were utilized: (1) diets in which the

caloric restriction was achieved by limiting the carbohydrate component only; (2) diets in which caloric restriction was achieved by reducing all components of the control ration (not necessarily in proportion to the caloric restriction); and (3) diets equivalent to the latter except that the fat content was increased by equicaloric substitution of fat for carbohydrate.

The results with all three series of diets confirm the introductory statement. Furthermore, it is demonstrated that the augmenting effect of a high fat diet on the formation of tumors occurs at all levels of caloric restriction studied. The results also suggest that caloric restriction achieved by limiting only the carbohydrate component of the diet may be more effective in inhibiting tumor formation than is caloric restriction achieved by restricting all components of the diet. Thus tumor formation is dependent on the composition of the diet, as well as the degree of caloric restriction.

Evidence is presented that the enhancing effect on tumor formation of a high fat diet, *ad libitum* or restricted, is due mainly to some specific action of fat. This action is independent of a general caloric effect that might be produced by the added consumption of the whole ration, carbohydrate, or fat.—Author's abstract.

Glyoxalase Activity of Liver from Rats Fed *p*-Dimethylaminoazobenzene. COHEN, P. P. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Cancer Research*, 5:626-630. 1945.

Livers from rats fed *p*-dimethylaminoazobenzene for a period up to 200 days showed a decreasing glyoxalase activity. The resulting liver tumors and transplants thereof showed about 10% of the glyoxalase activity of normal liver. The glyoxalase activity of regenerating rat liver showed no significant change from normal.—Author's abstract.

Glyoxalase Activity of Erythrocytes from Cancerous Rats and Human Subjects. COHEN, P. P., and SOBER, E. K. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Cancer Research*, 5:631-632. 1945.

Erythrocytes from patients with neoplastic and other diseases, and erythrocytes from rats with *p*-dimethylaminoazobenzene hepatomas and transplanted hepatomas showed no significant change in glyoxalase activity as compared with erythrocytes from normal subjects.—Authors' abstract.

Phosphorus Compounds in Animal Tissues. II. The Nucleic Acid Content of Homologous Normal and Cancer Tissues. SCHNEIDER, W. C. [Univ. of Wisconsin Med. Sch., Madison, Wis.] *Cancer Research*, 5:717-721. 1945.

The desoxypentose nucleic acid, the pentose nucleic acid, and the acid-soluble pentose contents of rat liver, rat hepatoma, mouse lung, and mouse lung tumor were determined. The desoxypentose nucleic acid content of both tumors was much greater than that of the homologous normal tissues. The pentose nucleic acid content of lung tumor was much greater than that of normal lung tissue, whereas the pentose nucleic acid content of liver and hepatoma was about the same. The acid-soluble, the lipid, and the protein phosphorus contents of rat hepatomas were found to be less than those of livers from rats on the same diet without the carcinogen, whereas the nucleic acid

phosphorus content of the hepatoma was higher than that of the liver. These findings are discussed in relation to the observations of other investigators.—Author's summary.

Tumors in Experimental Animals Receiving Steroid Hormones. GARDNER, W. U. [Yale Univ. Sch. of Med., New Haven, Conn.] *Surgery*, 16:8-32. 1944.

A review of the literature, and summary of the effects of estrogens on mammary, uterine, and testicular carcinogenesis, and of androgens and other steroid hormones on mammary tumors. A 5 page bibliography is appended.—W. A. B.

Experimental Investigations Concerning the Role of the Pituitary in Tumorigenesis. SELYE, H. [Montreal, Canada] *Surgery*, 16:33-46. 1944.

A review, with 122 references, on the effect on tumor formation of deficiency or excess of pituitary hormones, and on the formation of pituitary tumors, particularly in the anterior lobe, in animals treated with folliculoid compounds.—W. A. B.

The Effectiveness of Ovarian and Hypophysial Grafts in the Production of Mammary Carcinoma in Mice. LOEB, L., BLUMENTHAL, H. T., and KIRTZ, M. M. [Washington Univ. Sch. of Med., St. Louis, Mo.] *Science*, 99:230-232. 1944.

Ovaries, anterior pituitaries, or both were transplanted into 427 mice of several inbred strains. The findings in these were controlled by observations on 504 untreated mice. The effects of the implanted glands on the occurrence of mammary cancer were as follows:

Ovaries transplanted into castrated males stimulated the mammary gland to proliferate, secrete, and eventually develop cancer. If the anterior pituitaries were transplanted along with the ovaries, the tumor incidence was increased to as much as 92% (in strain A). A single combined transplantation of this sort was as effective as large doses of estrogen continued over long periods of time. In normal male mice these transplants had no effect on the mammary gland. Transplantation of ovaries alone into normal female mice led to the development of mammary cancer only in strains C3H and D, in which the mammary glands are very sensitive to hormonal stimulation. In the less sensitive strain A the ovarian grafts had no effect.

Transplantation of anterior pituitary was much more effective than ovarian transplantation in stimulating the development of tumors in normal females. Ovaries plus anterior pituitaries were as effective as or possibly more effective than anterior pituitaries alone. In ovariectomized mice the anterior pituitary transplants had little or no effect on the mammary glands. Therefore, it is thought that the anterior pituitary produces the effects described above through stimulation of estrogen production in the ovary.

In the susceptible mice the development of cancer was usually observed only after they had carried the transplants for 6 or 7 to 12 months. It is suggested that long continued stimulation of growth processes results finally in the elaboration of an autocatalytically propagating growth substance, which in turn is responsible for the cancerous growth. It was found that there was a parallelism between body weight and sensitivity to the hormones, the effective-

ness of the latter being greatest in mice belonging to the highest weight classes. Two conditions that inhibited or prevented the hormonal stimulation of mammary cancer development were as follows: (a) In certain strains (C57, CBA, Old Buffalo) the mammary tissue was not sufficiently sensitive to the hormones, probably because of lack of adequate amounts of milk factor, or because of genetic factors. (b) In other strains (AKA, New Buffalo) the individuality differentials were not sufficiently similar to allow successful grafting from one individual to another within a given strain.—R. B.

Characteristics of the Mammary Tumor Milk Agent in Serial Dilution and Blood Studies. BITTNER, J. J. [Univ. of Minnesota Med. Sch., Minneapolis, Minn.] *Proc. Soc. Exper. Biol. & Med.*, 59:43-44. 1945.

This report is concerned with the activity of the milk agent for mammary cancer in blood plasma, blood-cell suspensions, and serial dilution of extracts made from mammary tissue.

Blood was obtained from the hearts of mice carrying the agent. Either females of the A stock, 75 to 100 days of age, or females (A and C3H stocks and their hybrids) that had developed spontaneous mammary cancer were used. Cells and plasma were separated by centrifugation at 4,000 r.p.m. for 10 minutes, and the cells washed with saline several times. The cells for injection were suspended in saline, and the plasma was either undiluted or diluted in saline. The test animals were mice susceptible to mammary cancer and lacking the milk agent. They were injected intraperitoneally when from 3 to 5 weeks old.

Mice that received plasma from young donors developed 7% tumors, while mice that received the same volume of plasma derived from animals with spontaneous mammary cancer yielded 50% tumors. Mice injected with the cell suspension obtained from young donors gave 60% tumors; and those injected with the cell suspension from cancer-bearing mice gave 18%. Thus, although the results from young donors suggested that the agent might be within or on the blood cells, these preliminary results based on tumor mice were not confirmatory.

In other experiments, lactating mammary tissue was obtained from AZF₁ females that had had from 5 to 7 litters. The glands were macerated and serial dilutions made with triple distilled water. Each animal was injected intraperitoneally with 1 cc. of the suspension. Mice that received the more dilute suspension (1:5,000) yielded more tumors (46%) than those injected with less dilute (1:5) suspension (8%). This might be explained by (a) the presence of an inhibitory agent; (b) the destructive effect of autolyzing enzymes; (c) the development of active immunity with massive doses; or (d) genetic differences between hosts and donors.—M. B.

The Deterrent Effect of Light upon the Incidence of Spontaneous Mammary Cancer in Mice. APPERLY, F. L., and CARY, M. K. [Med. Coll. of Virginia, Richmond, Va.] *Cancer Research*, 5:698-704. 1945.

In an attempt to explain the fact that the cancer mortality rates in the various states and provinces of the United States and Canada vary inversely as the solar radiation and the number of people exposed thereto, mammary

cancer strain mice were exposed to light from a General Electric model F ultraviolet lamp for varying periods. Of mice that reached tumor age, 60 controls showed a cancer incidence of 40% when the experiment was terminated at the 131st week, while 101 mice exposed to ultraviolet radiation showed only 9% cancer incidence but the non-cancer death rate significantly increased. The application of specific death rates throughout the study gives a *P* value of 0.05 to 0.10, which indicates "probable significance." A study covering 98 weeks of observation gives a "significant" *P* value of 0.05. Vitamin D is apparently not a factor in these experiments. Other possible factors are discussed.—Authors' summary.

Attempts to Localize Tumor Metastases in Long Bones by Mechanical Trauma. SAPHIR, O., and LEVINTHAL, D. H. [Michael Reese Hosp., Chicago, Ill.] *Cancer Research*, 5:722-723. 1945.

In order to ascertain whether or not the Brown-Pearce carcinoma grows in long bones, transplants were made directly into the femur in 6 normal male rabbits. The tumor grew well within the marrow spaces in all, soon invaded the periosteum and adjacent muscles, and metastasized extensively.

Trauma to the long bones was produced by simple fracture of the humerus. In a series of 21 rabbits the left humerus was fractured and immediately afterward an injection of a suspension of tumor cells was made into the ear vein. In a second series of 12 rabbits the left humerus was fractured, and 14 days later a suspension of tumor cells was injected into the ear vein. In a third series of 12 animals, tumor was transplanted into the testes (for technic see *Am. J. Cancer*, 33:239-295. 1938). Two weeks later, after the testicular tumor was easily palpable, the left humerus was fractured.

Chronic irritation was produced by the placing of a vitallium screw immediately beneath the periosteum of the distal end of the femur. At a subsequent time a suspension of tumor cells was injected into the ear vein, or tumor was transplanted into the testes.

The results showed that mechanical trauma or chronic irritation of bones played no role in the localization of tumor metastases from transplanted Brown-Pearce carcinoma in rabbits.—Authors' abstract.

The Specificity of Acquired Tumor Immunity. GROSS, L. *J. Immunol.*, 50:91-99. 1945.

Mice of the C3H inbred line that had recovered spontaneously from an intracutaneously inoculated spindle cell sarcoma (Sa 1) were later found to be immune to Sa 1, but not to a rhabdomyosarcoma (Sa 2), nor to a mammary carcinoma (Ca 1), also inoculated intracutaneously. Both Sa 1 and Sa 2 had originally been induced with methylcholanthrene in C3H mice, and Ca 1 had originated spontaneously in an animal of the same line.

The results indicate that tumors may be immunologically different in spite of the fact that they originated in homozygous animals. It is postulated that tumor immunity is directed specifically against the immunizing tumor, as such, and is not caused by genetic differences between the cells of the host and those of the animal in which the tumor originated.

The following classification of tumor immunity is suggested: (1) *Natural*: inherited and lifelong, nonspecific, often destroyed by a suitable route of inoculation; (2) *Acquired* (as observed in animals that have recovered spontaneously from a successfully implanted neoplasm): generally strictly specific, lasting but not lifelong, limited (can be overwhelmed by large doses of the neoplasm) especially in males, acquired individually by animals originally susceptible, not necessarily accompanied by the presence of specific antibodies in the blood, and not transmissible by inheritance or by blood serum transfer.—M. H. P.

Reticuloendothelial Immune Serum (REIS). III. The Effect of Strong Concentrations on the Growth of Walker Rat Sarcoma 319 *in vitro*. POMERAT, C. M. [Univ. of Texas Med. Branch, Galveston, Texas] *Cancer Research*, 5:724-728. 1945.

Cells of Walker rat sarcoma 319 were inhibited *in vitro* by homologous (anti-rat) REIS but not by heterologous (anti-chick) REIS at similar concentrations. By the use of an anti-rat REIS with a complement-fixation titer of 1:1,600, sarcoma cells were inhibited at a concentration of 1:4 but not 1:16. Spleen cells were clumped and limited in migration by concentrations up to 1:256 but not at 1:512. Outgrowth of tumor was reduced, and cells were included in the medium, but this effect was not found for controls containing no REIS. It is suggested that the inhibitory action of spleen on tumor cells is exerted in the presence of relatively strong concentrations of REIS. These observations may explain results reported for the inhibition of tumor in eggs by spleen. In such cases the injected spleen may cause the developing chick to produce the necessary REIS factor.—Author's abstract.

The Development of Highly Malignant Tumor Strains from Naturally Occurring Avian Lymphomatosis. BURMEISTER, B. R., and PRICKETT, C. O. [U. S. Regional Poultry Research Lab., East Lansing, Mich.] *Cancer Research*, 5:652-660. 1945.

Young chicks injected intraperitoneally with affected organs of chickens with visceral lymphomatosis developed lymphomatous tumors of the viscera in a relatively short time.

Inocula prepared from different donors varied greatly in their activity. The material showing the greatest potency induced tumors in 13 of the 17 birds inoculated and caused death in an average of 11 days after inoculation. Organs that became involved included the abdominal wall, adrenal, gonad, heart, kidney, liver, mesentery, intestine, pancreas, peritoneum, proventriculus, and spleen. The least potent material, though grossly similar to the most potent, produced no tumors in 37 chicks injected during the experimental period of 86 days. Four inocula that elicited a high proportion of tumors were propagated by serial transfer through 15 to 19 passages made at intervals of 7 to 14 days. No essential differences in the gross pathology between the strains were noted.

The neoplastic cells, implanted in young chicks, will induce lymphoid tumors that are both macroscopically and microscopically similar to the tumors providing the original inoculum.

The question of transmission by a filterable agent has not yet been investigated.—Authors' summary.

Spontaneous Malignant Mixed Tumors of the Rat, and the Successful Transplantation and Separation of Both Components from a Breast Tumor. DUNNING, W. F., CURTIS, M. R., and MAUN, M. E. [Wayne Univ. Coll. of Med., and Detroit Inst. of Cancer Research, Detroit, Mich.] *Cancer Research*, 5:644-651. 1945.

Twenty-seven malignant mixed fibroepithelial spontaneous neoplasms involving the uterus, mammary gland, and face were discussed. At these sites both malignant epithelial and connective tissue tumors were frequent.

Metastases were examined in 10 of these cases. In 3 cases the secondary tumors were epithelial, in 1 only the sarcomatous element metastasized, and in 6 cases both components were identified in the secondary growths.

Transplantation studies of a spontaneous mammary neoplasm proved it to be a mixed tumor composed of malignant epithelium and mesothelium with each element showing independent segregation. After the fifth generation of transplantation the two components were separated and are being propagated as a pure adenocarcinoma in one series and an osteochondrosarcoma in the other.—Authors' abstract.

Clinical and Pathological Reports

Clinical investigations are sometimes included under Reports of Research

GENERAL

Endocrine Aspects of Cancer. NATHANSON, I. T. [Collis P. Huntington Memorial Hosp., Harvard Univ., and Massachusetts Gen. Hosp., Boston, and Pondville Hosp., Walpole, Mass.] *New England J. Med.*, 231:764-770; 795-802. 1944.

A review in the Medical Progress series, with 210 references. The first section deals with experimental tumors in animals, and the second with clinical observations.

The author concludes that although there is strong evidence that endocrine factors are associated with some human tumors, there is as yet no conclusive proof that these influences are directly concerned with cancer. The increasing number of cases coming to light in which cancer developed after intensive estrogen therapy is considered to be probably a coincidence, but one that cannot be ignored. The present evidence is interpreted as indicating that the sex hormones are not in themselves carcinogenic. "It is likelier that, as a result of excessive stimulation or atypical metabolism, the tissues of susceptible persons are conditioned to the action of a carcinogenic agent." In the author's opinion, there is little to support the therapeutic use of hormones in the treatment of any cancer except that of prostatic origin. Much more information must be obtained before assessing the value of treatment of cancer of the breast or other organs with either estrogens or androgens. Castration, however, is a useful adjunct to the treatment of selected cases of cancer of the breast as well as of the prostate, but such treatment should be reserved for palliative purposes only.—C. W.

Symposium on Endocrinology of Neoplastic Diseases—Introduction. TWOMBLY, G. H., and PACK, G. T. [New York, N. Y.] *Surgery*, 16:1-7. 1944.

The possible role of the hormones in producing and ameliorating neoplastic diseases in man and the lower animals is discussed briefly, and the commercial preparations available for use by surgeons are tabulated.—W. A. B.

SKIN AND SUBCUTANEOUS TISSUES

Solar Radiation and Pernicious Anemia in South Australia. THIERSCH, J. B. [Inst. of Med. and Vet. Sc., Adelaide, South Australia] *M. J. Australia*, 31:583. 1944.

Data are presented which suggest that the incidence of cancer of the skin is considerably greater in South Australia than it is in England. "That increase is mainly due to the greater solar radiation, as the localization of skin cancers on face and hands indicates."—E. L. K.

Malignant Papillary Cystadenoma of the Sweat Glands with Metastases to the Regional Lymph Nodes. HORN, R. C., JR. [Hosp. of Univ. of Pennsylvania, Philadelphia, Pa.] *Surgery*, 16:348-355. 1944.

A report of a cystadenoma of the sweat glands on the wrist in a man of 33, who had first noted the tumor 17 years before. Invasion of the radius and spread to axillary lymph nodes led to the decision to amputate the arm.—W. A. B.

NERVOUS SYSTEM

Morphologic Alterations of the Neuron Due to Tumor Invasion. STERN, K., and ODOM, G. L. [McGill Univ., and Montreal Neurol. Inst., Montreal, Canada] *Arch. Path.*, 39:221-225. 1945.

A study, at autopsy, of 36 gliomas of various kinds showed that intact neurons were present for varying depths within the invading tumors. The changes in cells and processes frequently encountered in vascular, toxic, and infective conditions were absent except when the neoplasms themselves had undergone secondary changes.—J. G. K.

Lipoma of the Brain. Report of Cases. EHNI, G. J., and ADSON, A. W. [Mayo Clin., Rochester, Minn.] *Arch. Neurol. & Psychiat.*, 53:299-304. 1945.

Two cases are reported and 69 from the literature are reviewed. In one of the new cases, the lipoma contained enough calcium to cast a shadow in the roentgenogram and was removed surgically.—M. E. H.

Neurinoma of the Facial Nerve. BOGDASARIAN, R. M. [Presbyterian Hosp., Binghamton, N. Y.] *Arch. Otolaryng.*, 40:291-294. 1944.

Report of a case in a 41 year old man whose earliest symptom was progressive deafness and who later had complete facial paralysis.—W. A. B.

BREAST

The Relationship of Hormones to Diseases of the Breast. NATHANSON, I. T. [Collis P. Huntington Memorial Hosp., and Massachusetts Gen. Hosp., Boston, Mass., and Pondville Hosp., Walpole, Mass.] *Surgery*, 16:108-140. 1944.

A review, with 132 references, of the role played by ovarian, testicular, pituitary, and adrenal hormones in diseases of the breast.—W. A. B.

The Effect of Sex Hormones on Skeletal Metastases from Breast Cancer. FARROW, J. H. [Memorial Hosp., New York, N. Y.] *Surgery*, 16:141-151. 1944.

A review with illustrative case reports and 25 references. Three cases are reported in which the effect of gonadal hormones on the skeletal metastases of breast cancer was observed. One patient, a woman of 26 years, received both estrone and testosterone propionate. Hypercalcemia was noted following each series of injections, and x-ray examinations showed progress of the osteolytic metastases. Similar extension of bone lesions was noted in a 63 year old male with breast cancer who received testosterone propionate. A third patient, also a male, had shown striking regression of both local lesion and skeletal metastases in 4 months following bilateral orchidectomy. A fourth case, in which cutaneous nodules in a woman with breast cancer showed a decrease in vascularity following castration, is cited as supporting the hypothesis that the mode of action of estrogens in stimulating bone metastases of mammary carcinoma may be through their vasodilating properties.—W. A. B.

Carcinoma of the Breast. PALETTA, F. X., and LEHMAN, E. P. [McIntyre Tumor Clin., and Univ. Hosp., Univ. of Virginia Sch. of Med., Charlottesville, Va.] *Surgery*, 15:944-953. 1944.

Two hundred and sixty-seven cases of carcinoma of the breast, seen at the University of Virginia Hospital since 1926, are reviewed. Comparison of carcinomas of the breast that metastasized to bone with those that involved viscera suggests a slightly greater degree of malignancy in the former.—W. A. B.

Mixed Malignancy of the Breast. Case Report of Combined Carcinoma and Sarcoma in a Child, with Review of the Literature. SMITHY, H. G. [Med. Coll. of State of South Carolina, Charleston, S. C.] *Surgery*, 16:854-864. 1944.

A case of mixed sarcoma and adenocarcinoma in a 10 year old girl is reported. A simple mastectomy was done, followed by deep x-ray therapy. The girl has been well 3 years and shows no sign of recurrence. The literature on similar mixed tumors is reviewed.—W. A. B.

FEMALE GENITAL TRACT

Ovarian Tumors with Sex Hormone Function. NOVAK, E. [Johns Hopkins Med. Sch., Baltimore, Md.] *Surgery*, 16:82-90. 1944.

A discussion, with bibliography, of the pathology and malignancy of the ovarian tumors, and of the endocrine

effects of both the feminizing and masculinizing groups.—W. A. B.

Endocrine Factors in the Origin of Tumors of the Uterus. TAYLOR, H. C., JR. [New York, N. Y.] *Surgery*, 16:91-107. 1944.

Endometrial hyperplasia, squamous metaplasia of the endometrium, carcinoma of the endometrium, fibroma uteri, adenomyosis, and cancer of the cervix, all can be produced in laboratory animals by hormonal agents; these are considered in relation to the morphologically similar tumors in women. The reasons for believing that the same etiological mechanisms operate in the human subjects as in lower animals are discussed.—W. A. B.

Double Pregnancy and Fibroids in a Duplex Uterus. Report of a Case. RILEY, E. A., and LEAHY, J. D. [Park Falls, Wis.] *Wisconsin M. J.*, 44:421. 1945.

The apparent difference in size of the fetuses suggested the possibility of superfetation, but evidence for proof is meager. The fibroids may have impaired the fetal nutrition and development.—M. E. H.

MALE GENITAL TRACT

Benign Hypertrophy and Carcinoma of the Prostate. MOORE, R. A. [Washington Univ. Sch. of Med., St. Louis, Mo.] *Surgery*, 16:152-165. 1944.

An analysis of statistical and experimental data supporting the hypothesis that benign hypertrophy and carcinoma of the prostate in man are caused by endocrinologic imbalance is presented, with a review of spontaneous and induced carcinoma of the prostate in the lower animals. A 3 page bibliography is included.—W. A. B.

The Endocrine Treatment of Cancers of the Prostate Gland. DEAN, A. L., WOODARD, H. Q., and TWOMBLY, G. H. [Memorial Hosp., New York, N. Y.] *Surgery*, 16:169-180. 1944.

The previous work on the relation of the gonadal hormones to cancer of the prostate is summarized, and the results of treatment of 100 patients, either by surgical castration or administration of stilbestrol, are reviewed. In both cases, an immediate, though often temporary, clinical improvement was observed. The serum acid phosphatase levels were determined as an aid in following the course of cancerous activity. Urinary hormone studies indicated that fundamentally different mechanisms are involved in the regressions produced by castration and by stilbestrol.—W. A. B.

The Relationship of Hormones to Testicular Tumors. TWOMBLY, G. H. [Memorial Hosp., New York, N. Y.] *Surgery*, 16:181-193. 1944.

A review of the literature on the production of testicular tumors by endocrine substances in the lower animals and man, and on the excretion of hormones by patients with testicular tumors. A survey of 135 of the author's cases confirms Hamburger's observation that chorionic gonadotropin appears in the urine of patients with active tumor only.—W. A. B.

URINARY SYSTEM—MALE AND FEMALE

Malignant Transformation in a Previously Benign Tubular Adenoma of the Kidney. BUCKLEY, W. [Victoria Hosp., Worksop, England] *Brit. J. Surg.*, **32**:315-319. 1944.

Description of a case.—E. L. K.

Épithélio-Sarcome du Rein Gauche, avec Fibro-Myo-Lipome du Même Rein, et Fibrome Théco-Cellulaire de l'Ovaire Homolatéral. Origine Rénale du Prétendu Hypernéphrome Vrai du Rein. [Carcino-Sarcoma of the Left Kidney, with Fibromyolipoma of the Same Kidney, and Theca-Cell Fibroma of the Homolateral Ovary. Renal Origin of the Alleged True Kidney Hypernephroma.] RIOPELLE, J. L. [Montreal Univ., Montreal, Canada] *Rev. canad. de biol.*, **4**:40-66. 1945.

In a female, 73 years of age, postmortem examination revealed a large complex tumor of the left kidney: the central portion was characteristic of "true kidney hypernephroma" and the peripheral zone, of fibrosarcoma. The sarcomatous portion alone gave rise to metastases. The cortex of the same kidney contained a small fibromyolipomatous inclusion and a pea-sized fibromyolipoma with a deep area of epithelial cells and spindle-shaped cells. Because of similarities in their cellular components, the inclusion is considered as a malformation (hamartia), the fibromyolipoma as the corresponding benign tumor (hamartoma), and the carcinosarcoma as the malignant equivalent (hamartoblastoma). In the left ovary a typical marble-sized theca-cell tumor was found.

The association of these three rare tumors supports the dysgenetic theory of their origin. Similarities between the fibromyolipoma and the carcinosarcoma indicate that "true kidney hypernephroma" may arise from the kidney and not necessarily from adrenal heterotopia.—C. A.

Sur les Tumeurs Rénales Connues sous le Nom d'Hypernéphromes Vrais. Théorie Rénale de leur Origine. [On Kidney Tumors Known as True Kidney Hypernephromas. The Theory of Their Renal Origin.] RIOPELLE, J. L. [Univ. of Montreal, Montreal, Canada] *Rev. canad. de biol.*, **4**:66-103. 1945.

Five personal, and 2 previously published cases (Masson and Simard, Stout) reported as instances of "true kidney hypernephroma" are reviewed. Five of the tumors are clear examples of true kidney hypernephroma and 2 are complex tumors (hypernephroma with squamous cell carcinoma of the pelvis, hypernephroma with true fasciculated sarcoma). All pure tumors and the hypernephromatous constituents of the complex ones are structurally similar to corticoadrenal carcinoma but present some glandular lumina and many gland-like formations. These facts and the results from the study of the mixed forms support the true renal nature and the dysgenetic origin of these growths. They may be ascribed to a disturbance in the early organogenesis of the metanephric blastema. The author proposes the term "metanephroma" for all kidney tumors that are morphologically similar to corticoadrenal carcinoma but genetically different. "True kidney hypernephroma" would be known as "paleogenetic metanephroma."—C. A.

ORAL CAVITY AND UPPER RESPIRATORY TRACT

Malignant Tumors of the Nasal Cavity. HAVENS, F. Z., and THORNELL, W. C. [Mayo Clin., Rochester, Minn.] *Arch. Otolaryng.*, **40**:396-401. 1944.

In removing malignant tumors of the nasal cavity that are shown by x-ray examination not to involve the bone, the authors have used a frontoethmoid approach in 8 cases, including carcinoma, squamous cell epithelioma, hemangio-endothelioma, adenocarcinoma, and unspecified types.—W. A. B.

Tumors of the Nose and Throat. NEW, G. B., and FOSS, E. L. [Mayo Clin., Rochester, Minn.] *Arch. Otolaryng.*, **40**:142-149. 1944.

A review of the literature of 1942 and 1943, with 42 references.—W. A. B.

Removal of a Frontal Osteoma and Correction of the Defect with a Tantalum Implant. CONLEY, J. J. *Arch. Otolaryng.*, **40**:295-297. 1944.

Report of a case of osteoma in the right frontal sinus. The tantalum implant had proved entirely satisfactory up to the time of the report, which was 9 months after the operation.—W. A. B.

Adamantinoma of the Maxillary Sinus. MOSHER, W. T. [Ventura, Calif.] *Arch. Otolaryng.*, **40**:61-62. 1944.

Report of a case and discussion of the origin of these tumors.—W. A. B.

Ossifying Fibroma of the Superior Maxilla. HARA, H. J. [White Memorial Hosp., Los Angeles, Calif.] *Arch. Otolaryng.*, **40**:180-188. 1944.

In the 3 cases reported, the tumors occurred in 2 women of 20 and 29 years, and in a boy of 14, and the first symptom was swelling of the cheek. X-ray examination is of aid in distinguishing the cancerous ossifying tumor from the noncancerous, since the contour of the latter is always smooth. Two of the tumors reported were well circumscribed and were completely removed.—W. A. B.

Extramedullary Plasma Cell Tumor of the Mouth. STANCIL, J. R., and TOMLINSON, W. J. [Gorgas Hosp., Ancon, Canal Zone] *Arch. Otolaryng.*, **40**:139-141. 1944.

Report of a case in a 26 year old male. The lesion, which was too extensive for surgical excision, has been controlled for 9 months by roentgen irradiation.—W. A. B.

The Pre-Epiglottic Space. Its Relation to Carcinoma of the Epiglottis. CLERF, L. H. [Jefferson Hosp., Philadelphia, Pa.] *Arch. Otolaryng.*, **40**:177-179. 1944.

The author believes that early invasion of the pre-epiglottic space by cancer of the epiglottis escapes detection by direct examination or by mirror laryngoscopy. Laryngectomy with extirpation of the pre-epiglottic space is recommended for carcinoma of the anterior portion of the larynx above the vocal cords.—W. A. B.

Cystadenoma of the Larynx. FIGI, F. A., ROWLAND, W. D., and NEW, G. B. [Mayo Clin., Rochester, Minn.] *Arch. Otolaryng.*, **40**:445-450. 1944.

Cystadenoma is a rare tumor in the larynx, occurring as a result of cystic degeneration in a simple adenoma, and producing signs of a slowly growing laryngeal tumor with progressive deafness. In 3 of the 4 cases presented, removal of the tumor was accomplished by means of suspension laryngoscopy.—W. A. B.

Carcinoma of the Larynx. HOWES, W. E., and PLATAU, M. [Brooklyn Cancer Inst., Brooklyn, N. Y.] *Arch. Otolaryng.*, **40**:133-138. 1944.

Seventy-seven cases of laryngeal carcinomas, seen at the Brooklyn Cancer Institute from 1934 through 1942, are reviewed, and the methods of therapy evaluated. Four surgical procedures were used in 18 patients: electrocoagulation, epiglottic resection, laryngofissure, and laryngectomy. The remaining patients received only radiotherapy. Only intrinsic carcinoma was successfully eradicated by surgical means. Recurrence followed electrocoagulation in all cases. Among 43 patients treated with irradiation alone, 10 are still living.—W. A. B.

Hemangioma of the Adult and of the Infant Larynx. FERGUSON, G. B. [Durham, N. C.] *Arch. Otolaryng.*, **40**:189-195. 1944.

In an infant of 7 weeks who had a small hemangioma of the larynx causing intermittent obstruction, treatment was tracheotomy followed by irradiation. The adult, a 20 year old male, was given irradiation by radon implants, but future excision is contemplated.—W. A. B.

Cancer of the Trachea. FISHER, G. E. [Birmingham, Ala.] *Arch. Otolaryng.*, **40**:49-51. 1944.

Five cases are reported in which bronchoscopy followed by biopsy revealed adenocarcinoma, epithelioma, or squamous cell carcinoma of the trachea. In 2 of these, the growth was treated with electrocoagulation through a bronchoscope, and subsequent x-irradiation.—W. A. B.

INTRATHORACIC TUMORS—LUNGS—PLEURA

Bronchial Adenoma with Metastasis. LAFF, H. I., and NEUBERGER, K. T. [Univ. of Colorado Sch. of Med. and Hosps., Denver, Colo.] *Arch. Otolaryng.*, **40**:487-493. 1944.

A slowly growing tumor of the bronchus, diagnosed as adenoma 13½ years before the death of the patient, finally caused death by extensive metastases to the opposite lung. In a second patient, the lung was involved 1 year following the observation, by means of bronchoscopy, of a growth in the bronchus. The authors feel that bronchial adenoma should not be treated as a benign tumor and might better be called "bronchial carcinoid" as has been previously suggested.—W. A. B.

Roentgenologic and Pathologic Aspects of Pulmonary Tumors Probably Alveolar in Origin. GEEVER, E. F., CARTER, H. R., NEUBERGER, K. T., and SCHMIDT, E. A. [Univ. of Colorado Sch. of Med. and Hosps., Denver, Colo.] *Radiology*, **44**:319-327. 1945.

Six cases of probable primary pulmonary alveolar cell carcinoma are presented, one of which was complicated by torulosis of the central nervous system. The roentgen appearance is not diagnostic; differential diagnosis from primary bronchogenic carcinoma, metastatic disease, fungous infections, tuberculosis, and pneumonitis must be made. If, from the clinical picture, neoplasm is suspected

and no other primary is found, this type of neoplasm should be considered.—R. E. S.

Cavernous Hemangioma of the Lung. (Arterio-venous Fistula). ADAMS, W. E., THORNTON, T. F., JR., and EICHELBERGER, L. *Arch. Surg.*, **49**:51-58. 1944.

The patient, a 24 year old man, had had complaints of cyanosis, clubbing of fingers, and frequent nosebleeds for years. There were polycythemia, polyemia, and hyperhemoglobinemia. After pneumonectomy for removal of the cavernous hemangioma in the left lung, the blood picture approached normal, and the patient returned to work.—W. A. B.

LIVER AND GALL BLADDER

Papilloma of the Gall Bladder. GREENWALD, W. [New York, N. Y.] *Surgery*, **16**:370-376. 1944.

Two cases of papilloma of the gall bladder, occurring in women of 46 and 36 years of age, are discussed. The diagnosis was suggested preoperatively by roentgen examination.—W. A. B.

Congenital Cyst of the Common Bile-Duct Containing Stones and Undergoing Cancerous Change. IRWIN, S. T., and MORISON, J. E. [Roy. Victoria Hosp., Belfast, Ireland] *Brit. J. Surg.*, **32**:319-321. 1944.

Description of a case.—E. L. K.

The Surgical Treatment of Carcinoma of the Common Bile Duct. PICKRELL, K. L., and BLALOCK, A. [Johns Hopkins Univ. and Hosp., Baltimore, Md.] *Surgery*, **15**:923-937. 1944.

Two cases of carcinoma of the common bile duct are reported. In the first patient, a 60 year old man, a resection of the common duct was performed, with choledochoduodenostomy and cholecystectomy. The second man, 67 years old, was subjected to pancreatoduodenectomy with implantation of the pancreatic duct into the duodenum. Both patients were apparently well 18 months and 7 months after operation. The previous surgical procedures for the removal of lesions in this site are discussed, and the cases reported since 1902 tabulated.—W. A. B.

BONE AND SYNOVIAL MEMBRANE

Progress in Orthopedic Surgery for 1943. V. Tumors of Bone and of Synovial Membrane. MEYERDING, H. W., ET AL. [Rochester, Minn.] *Arch. Surg.*, **49**:198-209. 1944.

A review, including several classifications of bone tumors.—W. A. B.

Osteoid Osteoma. KLEINBERG, S. [New York, N. Y.] *Am. J. Surg.*, **66**:396-401. 1944.

The author discusses this tumor and presents 3 cases in subjects from 10 to 17 years of age, all manifesting the triad of localized pain, tenderness, and a rarefaction of bone demonstrable by x-ray examination at the site of pain and tenderness.—W. A. B.

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